Figure 1 (A)

```
GAATTCGGCTTCCATCCTAATACGACTCACTATAGGGCTCGAGCGGCCGCCCGGGGCAGGTATCTTGGCTCACAGGGGA   79

    M   S   S   S   S   W   L   L   L   S   L   V   A   V   T   A   A   Q   S      19
CG ATG TCA AGC TCT TCC TGG CTC CTT CTC AGC CTT GTT GCT GTA ACT GCT GCT CAG TCC     138

 T   I   E   E   Q   A   K   T   F   L   D   K   F   N   H   E   A   E   D   L     39
ACC ATT GAG GAA CAG GCC AAG ACA TTT TTG GAC AAG TTT AAC CAC GAA GCC GAA GAC CTG    198

 F   Y   Q   S   S   L   A   S   W   N   Y   N   T   N   I   T   E   E   N   V     59
TTC TAT CAA AGT TCA CTT GCT TCT TGG AAT TAT AAC ACC AAT ATT ACT GAA GAG AAT GTC    258
          intron1
 Q   N   M   N   N   A   G   D   K   W   S   A   F   L   K   E   Q   S   T   L     79
CAA AAC ATG AAT AAT GCT GGG GAC AAA TGG TCT GCC TTT TTA AAG GAA CAG TCC ACA CTT    318

 A   Q   M   Y   P   L   Q   E   I   Q   N   L   T   V   K   L   Q   L   Q   A     99
GCC CAA ATG TAT CCA CTA CAA GAA ATT CAG AAT CTC ACA GTC AAG CTT CAG CTG CAG GCT    378
                                                  intron2
 L   Q   Q   N   G   S   S   V   L   S   E   D   K   S   K   R   L   N   T   I    119
CTT CAG CAA AAT GGG TCT TCA GTG CTC TCA GAA GAC AAG AGC AAA CGG TTG AAC ACA ATT    438

 L   N   T   M   S   T   I   Y   S   T   G   K   V   C   N   P   D   N   P   Q    139
CTA AAT ACA ATG AGC ACC ATC TAC AGT ACT GGA AAA GTT TGT AAC CCA GAT AAT CCA CAA    498
                  intron3
 E   C   L   L   L   E   P   G   L   N   E   I   M   A   N   S   L   D   Y   N    159
GAA TGC TTA TTA CTT GAA CCA GGT TTG AAT GAA ATA ATG GCA AAC AGT TTA GAC TAC AAT    558

 E   R   L   W   A   W   E   S   W   R   S   E   V   G   K   Q   L   R   P   L    179
GAG AGG CTC TGG GCT TGG GAA AGC TGG AGA TCT GAG GTC GGC AAG CAG CTG AGG CCA TTA    618
                                                      intron4
 Y   E   E   Y   V   V   L   K   N   E   M   A   R   A   N   H   Y   E   D   Y    199
TAT GAA GAG TAT GTG GTC TTG AAA AAT GAG ATG GCA AGA GCA AAT CAT TAT GAG GAC TAT    678

 G   D   Y   W   R   G   D   Y   E   V   N   G   V   D   G   Y   D   Y   S   R    219
GGG GAT TAT TGG AGA GGA GAC TAT GAA GTA AAT GGG GTA GAT GGC TAT GAC TAC AGC CGC    738

 G   Q   L   I   E   D   V   E   H   T   F   E   E   I   K   P   L   Y   E   H    239
GGC CAG TTG ATT GAA GAT GTG GAA CAT ACC TTT GAA GAG ATT AAA CCA TTA TAT GAA CAT    798

 L   H   A   Y   V   R   A   K   L   M   N   A   Y   P   S   Y   I   S   P   I    259
CTT CAT GCC TAT GTG AGG GCA AAG TTG ATG AAT GCC TAT CCT TCC TAT ATC AGT CCA ATT    858
                      intron5
 G   C   L   P   A   H   L   L   G   D   M   W   G   R   F   W   T   N   L   Y    279
GGA TGC CTC CCT GCT CAT TTG CTT GGT GAT ATG TGG GGT AGA TTT TGG ACA AAT CTG TAC    918

 S   L   T   V   P   F   G   Q   K   P   N   I   D   V   T   D   A   M   V   D    299
TCT TTG ACA GTT CCC TTT GGA CAG AAA CCA AAC ATA GAT GTT ACT GAT GCA ATG GTG GAC    978
intron6
 Q   A   W   D   A   Q   R   I   F   K   E   A   E   K   F   F   V   S   V   G    319
CAG GCC TGG GAT GCA CAG AGA ATA TTC AAG GAG GCC GAG AAG TTC TTT GTA TCT GTT GGT   1038

 L   P   N   M   T   Q   G   F   W   E   N   S   M   L   T   D   P   G   N   V    339
CTT CCT AAT ATG ACT CAA GGA TTC TGG GAA AAT TCC ATG CTA ACG GAC CCA GGA AAT GTT   1098
                                  intron7
 Q   K   A   V   C   H   P   T   A   W   D   L   G   K   G   D   F   R   I   L    359
CAG AAA GCA GTC TGC CAT CCC ACA GCT TGG GAC CTG GGG AAG GGC GAC TTC AGG ATC CTT   1158

 M   C   T   K   V   T   M   D   D   F   L   T   A   H   H   E   M   G   H   I    379
ATG TGC ACA AAG GTG ACA ATG GAC GAC TTC CTG ACA GCT CAT CAT GAG ATG GGG CAT ATC   1218

 Q   Y   D   M   A   Y   A   A   Q   P   F   L   L   R   N   G   A   N   E   G    399
CAG TAT GAT ATG GCA TAT GCT GCA CAA CCT TTT CTG CTA AGA AAT GGA GCT AAT GAA GGA   1278

 F   H   E   A   V   G   E   I   M   S   L   S   A   A   T   P   K   H   L   K    419
TTC CAT GAA GCT GTT GGG GAA ATC ATG TCA CTT TCT GCA GCC ACA CCT AAG CAT TTA AAA   1338
                                          intron8
 S   I   G   L   L   S   P   D   F   Q   E   D   N   E   T   E   I   N   F   L    439
TCC ATT GGT CTT CTG TCA CCC GAT TTT CAA GAA GAC AAT GAA ACA GAA ATA AAC TTC CTG   1398

 L   K   Q   A   L   T   I   V   G   T   L   P   F   T   Y   M   L   E   K   W    459
CTC AAA CAA GCA CTC ACG ATT GTT GGG ACT CTG CCA TTT ACT TAC ATG TTA GAG AAG TGG   1458

 R   W   M   V   F   K   G   E   I   P   K   D   Q   W   M   K   K   W   W   E    479
AGG TGG ATG GTC TTT AAA GGG GAA ATT CCC AAA GAC CAG TGG ATG AAA AAG TGG TGG GAG   1518
```

ZBD

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Figure 1(B)

```
intron 9
 M   K | R   E   I   V   G   V   V   E   P   V   P   H   D   E   T   Y   C   D    499
ATG AAG|CGA GAG ATA GTT GGG GTG GTG GAA CCT GTG CCC CAT GAT GAA ACA TAC TGT GAC  1578
                                                         intron 10
 P   A   S   L   F   H   V   S   N   D   Y   S   F   I   R | Y   Y   T   R   T    519
CCC GCA TCT CTG TTC CAT GTT TCT AAT GAT TAC TCA TTC ATT CG|A TAT TAC ACA AGG ACC  1638

 L   Y   Q   F   Q   F   Q   E   A   L   C   Q   A   A   K   H   E   G   P   L    539
CTT TAC CAA TTC CAG TTT CAA GAA GCA CTT TGT CAA GCA GCT AAA CAT GAA GGC CCT CTG  1698
                                                             intron 11
 H   K   C   D   I   S   N   S   T   E   A   G   Q   K   L | F   N   M   L   R    559
CAC AAA TGT GAC ATC TCA AAC TCT ACA GAA GCT GGA CAG AAA CTG|TTC AAT ATG CTG AGG  1758

 L   G   K   S   E   P   W   T   L   A   L   E   N   V   V   G   A   K   N   M    579
CTT GGA AAA TCA GAA CCC TGG ACC CTA GCA TTG GAA AAT GTT GTA GGA GCA AAG AAC ATG  1818

 N   V   R   P   L   L   N   Y   F   E   P   L   F   T   W   L   K   D   Q   N    599
AAT GTA AGG CCA CTG CTC AAC TAC TTT GAG CCC TTA TTT ACC TGG CTG AAA GAC CAG AAC  1878
                                                 intron 12
 K   N   S   F   V   G   W   S   T   D   W   S   P | Y   A   D   Q   S   I   K    619
AAG AAT TCT TTT GTG GGA TGG AGT ACC GAC TGG AGT CC|A TAT GCA GAC CAA AGC ATC AAA  1938
                                                   intron 13
 V   R   I   S   L   K   S   A   L   G   D   K   A | Y   E   W   N   D   N   E    639
GTG AGG ATA AGC CTA AAA TCA GCT CTT GGA GAT AAA GC|A TAT GAA TGG AAC GAC AAT GAA  1998

 M   Y   L   F   R   S   S   V   A   Y   A   M   R   Q   Y   F   L   K   V   K    659
ATG TAC CTG TTC CGA TCA TCT GTT GCA TAT GCT ATG AGG CAG TAC TTT TTA AAA GTA AAA  2058
                             intron 14
 N   Q   M   I   L   F   G | E   E   D   V   R   V   A   N   L   K   P   R   I    679
AAT CAG ATG ATT CTT TTT GGG|GAG GAG GAT GTG CGA GTG GCT AAT TTG AAA CCA AGA ATC  2118

 S   F   N   F   F   V   T   A   P   K   N   V   S   D   I   I   P   R   T   E    699
TCC TTT AAT TTC TTT GTC ACT GCA CCT AAA AAT GTG TCT GAT ATC ATT CCT AGA ACT GAA  2178
                         intron 15
 V   E   K   A   I   R | M   S   R   S   R   I   N   D   A   F   R   L   N   D    719
GTT GAA AAG GCC ATC AGG|ATG TCC CGG AGC CGT ATC AAT GAT GCT TTC CGT CTG AAT GAC  2238

 N   S   L   E   F   L   G   I   Q   P   T   L   G   P   P   N   Q   P   F   V    739
AAC AGC CTA GAG TTT CTG GGG ATA CAG CCA ACA CTT GGA CCT CCT AAC CAG CCC CCT GTT  2298

 S  [I   W   L   I   V   F   G   V   V   M   G   V   I   V   V   G   I   V   I    759
TCC [ATA TGG CTG ATT GTT TTT GGA GTT GTG ATG GGA GTG ATA GTG GTT GGC ATT GTC ATC  2358  TMD
                                             intron 16
 L   I   F   T   G   I]  R   D   R   K   K | K   N   K   A   R   S   G   E   N    779
CTG ATC TTC ACT GGG ATC] AGA GAT CGG AAG AAG|AAA AAT AAA GCA AGA AGT GGA GAA AAT  2418

 P   Y   A   S   I   D   I   S   K   G   E   N   N   P   G   F   Q   N   T   D    799
CCT TAT GCC TCC ATC GAT ATT AGC AAA GGA GAA AAT AAT CCA GGA TTC CAA AAC ACT GAT  2478

 D   V   Q   T   S   F   *                                                        806
GAT GTT CAG ACC TCC TTT TAG                                                      2499

AAAAATCTATGTTTTTCCTCTTGAGGTGATTTTGTTGTATGTAAATGTTAATTTCATGGTATAGAAAATATAAGATGAT  2578
AAAGATATCATTAAATGTCAAAACTATGACTCTGTTCAGAAAAAAAATTGTCGAAAGACAACATGGCCAAGGAGAGAGC  2657
ATCTTCATTGACATTGCTTTCAGTATTTATTTCTGTCTCTGGATTTGACTTCTGTTCTGTTTCTTAATAAGGATTTTGT  2736
ATTAGAGTATATTAGGGAAAGTGTGTATTTGGTCTCACAGGCTGTTCAGGGATAATCTAAATGTAAATGTCTGTTGAAT  2815
TTCTGAAGTTGAAAACAAGGATATATCATTGGAGCAAGTGTTGGATCTTGTATGGAATATGGATGGATCACTTGTAAGG  2894
ACAGTGCCTGGGAACTGGTGTAGCTGCAAGGATTGAGAATGGCATGCATTAGCTCACTTTCATTTAATCCATTGTCAAG  2973
GATGACATGCTTTCTTCACAGTAACTCAGTTCAAGTACTATGGTGATTTGCCTACAGTGATGTTTGGAATCGATCATGC  3052
TTTCTTCAAGGTGACAGGTCTAAAGAGAGAAGAATCCAGGGAACAGGTAGAGGACATTGCTTTTTCACTTCCAAGGTGC  3131
TTGATCAACATCTCCCTGACAACACAAAACTAGAGCCAGGGGCCTCCGTGAACTCCCAGAGCATGCCTGATAGAAACTC  3210
ATTTCTACTGTTCTCTAACTGTGGAGTGAATGGAAATTCCAACTGTATGTTCACCCTCTGAAGTGGGTACCCAGTCTCT  3289
TAAATCTTTTGTATTTGCTCACAGTGTTTGAGCAGTGCTGAGCACAAAGCAGACACTCAATAAATGCTAGATTTACACA  3368
CTC|AAAAAAAAAAAAAAAAGGGCGGCCGC                                                   3396
intron 17
```

Figure 2 (A)

```
ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      MGAASGRRGPGLLLPLP-----LLLLL-PPQPALALDPGLQPGNFSADEAGAQLFAQSYN
mu-ACE      MGAASGQRGRWPLSPPLLMLSLLVLLLQP-SPAPALDPGLQPGNFSPDEAGAQLFAESYN
rat-ACE     MGAASGQRGRWPLSPPLLMLSLLLLLLLPPSPAPALDPGLQPGNFSADEAGAQLFADSYN
rb-ACE      MGAAPGRRGPRLLRPPPPLL-LLLLLLRPPPAALTLDPGLLPGDFAADEAGARLFASSYN

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      SSAEQVLFQSVAASWAHDTNITAENARRQEEAALLSQEFAEAWGQKAKELYEPIWQNFTD
mu-ACE      SSAEVVMFQSTVASWAHDTNITEENARRQEEAALVSQEFAEVWGKKAKELYESIWQNFTD
rat-ACE     SSAEVVMFQSTAASWAHDTNITEENARLQEEAALINQEFAEVWGKKAKELYESIWQNFTD
rb-ACE      SSAEQVLERSTAASWAHDTNITAENARRQEEEALLSQEFAEAWGRRLRSSMTRCGRTSPT

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      PQLRRIIGAVRTLGSANLPLAKRQQYNALLSNMSRIYSTAKVCLPNKTATCWSLDPDLTN
mu-ACE      SKLRRIIGSIRTLGPANLPLAQRQQYNSLLSNMSRIYSTGKVCFPNKTATCWSLDPELTN
rat-ACE     QKLRRIIGSVQTLGPANLPLTQRLQYNSLLSNMSRIYSTGKVCFPNKTATCWSLDPELTN
rb-ACE      QSCAGSSGLCAPWPCQPAP-GQAAADNSLLSNMSQIYSTGRSASPTRLPAAWSLDPDLNN

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      ILASSRSYAMLLFAWEGWHNAAGIPLKPLYEDFTALSNEAYKQDGFTDTGAYWRSWYNSP
mu-ACE      ILASSRSYAKLLFAWEGWHDAVGIPLKPLYQDFTAISNEAYRQDDFSDTGAFWRSWYESP
rat-ACE     ILASSRNYAKVLFAWEGWHDAVGIPLRPLYQDFTALSNEAYRQDGFSDTGAYWRSWYESP
rb-ACE      ILASSRSYAMLLFAWEGWHNAVGIPLKPLYQEFTALSNEAYRQDGFSDTGAYWRSWYDSP

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      TFEDDLEHLYQQLEPLYLNLHAFVRRALHRRYGDRYINLRGPIPAHLLGDMWAQSWENIY
mu-ACE      SFEESLEHIYHQLEPLYLNLHAYVRRALHRRYGDKYVNLRGPIPAHLLGDMWAQSWENIY
rat-ACE     SFEESLEHLYHQVEPLYLNLHAFVRRALHRRYGDKYINLRGPIPAHLLGDMWAQSWENIY
rb-ACE      TFEEDLERIYHQLEPLYLNLHAYVRRVLHRRYGDRYINLRGPIPAHLLGNMWAQSWESIY

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      DMVVPFPDKPNLDVTSTMLQQGWNATHMFRVAEEFFTSLELSPMPPEFWEGSMLEKPADG
mu-ACE      DMVVPFPDKPNLDVTSTMVQKGWNATHMFRVSEEFFTSLGLSPMPPEFWAESMLEKPTDG
rat-ACE     DMVVPFPDKPNLDVTSTMVQKGWNATHMFRVAEEFFTSLGLSPMPPEFWAESMLEKPADG
rb-ACE      DMVVPFPDKPNLDVTSTMVQKGWNATHMFRVAEEFFTSLGLLPMPPEFWAESMLEKPEDG

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      REVVCHASAWDFYNRKDFRIKQCTRVTMDQLSTVHHEMGHIQYYLQYKDLPVSLRRGANP
mu-ACE      REVVCHASAWDFYNRKDFRIKQCTRVTMEQLATVHHEMGHVQYYLQYKDLHVSLRRGANP
rat-ACE     REVVCHASAWDFYNRKDFRIKQCTRVTMDQLSTVHHEMGHVQYYLQYKDLHVSLRRGANP
rb-ACE      REVVCHASAWDFYNRKDFRIKQCTQVTMDQLSTVHHEMGHVQYYLQYKDQPVSLRR-ANP
```

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Figure 2 (B)

```
ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      GFHEAIGDVLALSVSTPEHLHKIGLLDRVTNDTESDINYLLKMALEKIAFLPFGYLVDQW
mu-ACE      GFHEAIGDVLALSVSTPAHLHKIGLLDHVTNDIESDINYLLKMALEKIAFLPFGYLVDQW
rat-ACE     GFHEAIGDVLALSVSTPAHLHKIGLLDRVANDIESDINYLLKMALEKIAFLPFGYLVDQW
rb-ACE      GFHEAIGDVLALSVSTPAHLHKIGLLDHVTNDTESDINYLLKMALEKIAFLPFGYLVDQW

ace-2       ------------------------------------------------------------
hu-ACET     ------------------------------------------------------------
mu-ACET     ------------------------------------------------------------
rb-ACET     ------------------------------------------------------------
hu-ACE      RWGVFSGRTPPSRYNFDWWYLRTKYQGICPPVTRNETHFDAGAKFHVPNVTPYIRYFVSF
mu-ACE      RWGVFSGRTPPSRYNFDWWYLRTKYQGICPPVARNETHFDAGAKFHIPNVTPYIRYFVSF
rat-ACE     RWGVFSGRTPPSRYNYDWWYLRTKYQGICPPVARNETHFDAGAKFHIPSVTPYIRYFVSF
rb-ACE      RWGVFSGRTPSSRYNFDWWYLRTKYQGICPPVVRNETHFDAGAKFHIPSVTPYIRYFVSF

ace-2       ------------------------------------------------------------
hu-ACET     ----------------------------------------MGQGWATAGLPSLLFLLLC
mu-ACET     ----------------------------------------MGQGWATPGLPSFLFLL---LC
rb-ACET     ----------------------------------------MGQGWAAPGLPSLLLLLLCCGHSLL
hu-ACE      VLQFQFHEALCKEAGYEGPLHQCDIYRSTKAGAKLRKVLQAGSSRPWQEVLKDMVGLDAL
mu-ACE      VLQFQFHQALCKEAGHQGPLHQCDIYQSTQAGAKLKQVLQAGCSRPWQEVLKDLVGSDAL
rat-ACE     VLQFQFHQALCKEAGHQGPLHQCDIYQSTKAGAKLQQVLQAGCSRPWQEVLKDLVGSDAL
rb-ACE      VLQFQFHQALCMEAGHQGPLHQCDIYQSTRAGAKLRAVLQAGCSRPWQEVLKDMVASDAL

ace-2       ----------------------------MSSSSWLLLSLVAVTAA---QSTIEEQAKTFL
hu-ACET     YGHPLLVPSQEASQQVTVTHGTSSQATTSSQTTTHQATAHQTSAQSPNLVTDEAEASKFV
mu-ACET     CGHHLLVLSQVATDHVTANQGITNQATTRSQTTTHQATIDQTTQI-PNLETDEAKADRFV
rb-ACET     VPSRVAARRVTVNQGTTSQATTTSKATTSIRATTHQTTAHQTTQS-PNLVTDEAEASRFV
hu-ACE      DAQPLLKYFQPVTQWLQEQNQQNGEVLGWPEYQWHPPLPDNYPEG-IDLVTDEAEASKFV
mu-ACE      DAKALLEYFQPVSQWLEEQNQRNGEVLGWPENQWRPPLPDNYPEG-IDLETDEAKADRFV
rat-ACE     DASALMEYFQPVSQWLQEQNQRNGEVLGWPEYQWRPPLPDNYPEG-IDLETDEAKANRFV
rb-ACE      DAQPLLDYFQPVTQWLQEQNERNGEVLGWPEYQWRPPLPNNYPEG-IDLVTDEAEASRFV
                                                          . * * :*. *:

ace-2       DKFNHEAEDLFYQSSLASWNYNTNITEENVQNMNNAGDKWSAFLKEQSTLAQMYPLQEIQ
hu-ACET     EEYDRTSQVVWNEYAEANWNYNTNITTETSKILLQKNMQIANHTLKYGTQARKFDVNQLQ
mu-ACET     EEYDRTAQVLLNEYAEANWQYNTNITIEGSKILLEKSTEVSNHTLKYGTRAKTFDVSNFQ
rb-ACET     EEYDRSFQAVWNEYAEANWNYNTNITTEASKILLQKNMQIANHTLTYGNWARRFDVSNFQ
hu-ACE      EEYDRTSQVVWNEYAEANWNYNTNITTETSKILLQKNMQIANHTLKYGTQARKFDVNQLQ
mu-ACE      EEYDRTAQVLLNEYAEANWQYNTNITIEGSKILLEKSTEVSNHTLKYGTRAKTFDVSNFQ
rat-ACE     EEYDRTAKVLWNEYAEANWHYNTNITIEGSKILLQKNKEVSNHTLKYGTWAKTFDVSNFQ
rb-ACE      EEYDRSFQAVWNEYAEANWNYNTNITTEASKILLQKNMQIANHTLTYGNWARRFDVSNFQ
            ::::: : :  : .: *.*:****** * : : : :.: : .    .. *: : :.::*

ace-2       NLTVKLQLQALQQNGSSVLSEDKSKRLNTILNTMSTIYSTGKVCNPDNPQECLLLEPGLN
hu-ACET     NTTIKRIIKKVQDLERAALPAQELEEYNKILLDMETTYSVATVCHPNG--SCLQLEPDLT
mu-ACET     NSSIKRIIKKLQNLDRAVLPPKELEEYNQILLDMETTYSLSNICYTNG--TCMPLEPDLT
rb-ACET     NATSKRIIKKVQDLQRAVLPVKELEEYNQILLDMETIYSVANVCRVDG--SCLQLEPDLT
hu-ACE      NTTIKRIIKKVQDLERAALPAQELEEYNKILLDMETTYSVATVCHPNG--SCLQLEPDLT
mu-ACE      NSSIKRIIKKLQNLDRAVLPPKELEEYNQILLDMETTYSLSNICYTNG--TCMPLEPDLT
rat-ACE     NSTIKRIIKKVQNVDRAVLPPNELEEYNQILLDMETTYSVANVCYTNG--TCLSLEPDLT
rb-ACE      NATSKRIIKKVQDLQRAVLPVKELEEYNQILLDMETIYSVANVCRVDG--SCLQLEPDLT
            * : *  :: :*:   :.*. .: :. * **  *.* ** ..:*  :.   *: ***.*.

ace-2       EIMANSLDYNERLWAWESWRSEVGKQLRPLYEEYVVLKNEMARANHYEDYGDYWRGDYEV
hu-ACET     NVMATSRKYEDLLWAWEGWRDKAGRAILQFYPKYVELINQAARLNGYVDAGDSWRSMYET
mu-ACET     NMMATSRKYEELLWAWKSWRDKVGRAILPFFPKYVEFSNKIAKLNGYTDAGDSWRSLYES
rb-ACET     NLMATSRKYDELLWVWTSWRDKVGRAILPYFPKYVEFTNKAARLNGYVDAGDSWRSMYET
hu-ACE      NVMATSRKYEDLLWAWEGWRDKAGRAILQFYPKYVELINQAARLNGYVDAGDSWRSMYET
mu-ACE      NMMATSRKYEELLWAWKSWRDKVGRAILPFFPKYVEFSNKIAKLNGYTDAGDSWRSLYES
rat-ACE     NIMATSRKYEELLWVWKSWRDKVGRAILPFFPKYVDFSNKIAKLNGYSDAGDSWRSSYES
rb-ACE      NLMATSRKYDELLWVWTSWRDKVGRAILPYFPKYVEFTNKAARLNGYVDAGDSWRSMYET
            ::**.* .*:: **.* .**.:.*: :   : :** : *: *: * * * ** **. **
```

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Figure 2 (C)

```
ace-2       NGVDGYDYSRGQLIEDVEHTFEEIKPLYEHLHAYVRAKLMNAY-PSYISPIGCLPAHLLG
hu-ACET     P----------SLEQDLERLFQELQPLYLNLHAYVRRALHRHYGAQHINLEGPIPAHLLG
mu-ACET     D----------NLEQDLEKLYQELQPLYLNLHAYVRRSLHRHYGSEYINLDGPIPAHLLG
rb-ACET     P----------TLEQDLERLFQELQPLYLNLHAYVGRALHRHYGAQHINLEGPIPAHLLG
hu-ACE      P----------SLEQDLERLFQELQPLYLNLHAYVRRALHRHYGAQHINLEGPIPAHLLG
mu-ACE      D----------NLEQDLEKLYQELQPLYLNLHAYVRRSLHRHYGSEYINLDGPIPAHLLG
rat-ACE     D----------DLEQDLEKLYQELQPLYLNLHAYVRRSLHRHYGSEYINLDGPIPAHLLG
rb-ACE      P----------TLEQDLERLFQELQPLYLNLHAYVGRALHRHYGAQHINLEGPIPAHLLG
                        * :*:*: ::*::*** :***** * . * ..:*. * :*******

ace-2       DMWGRFWTNLYSLTVPFGQKPNIDVTDAMVDQAWDAQRIFKEAEKFFVSVGLPNMTQGFW
hu-ACET     NMWAQTWSNIYDLVVPFPSAPSMDTTEAMLKQGWTPRRMFKEADDFFTSLGLLPVPPEFW
mu-ACET     NMWAQTWSNIYDLVAPFPSAPNIDATEAMIKQGWTPRRIFKEADNFFTSLGLLPVPPEFW
rb-ACET     NMWAQTWSNIYDLVAPFPSASTMDATEAMIKQGWTPRRMFEEADKFFISLGLLPVPPEFW
hu-ACE      NMWAQTWSNIYDLVVPFPSAPSMDTTEAMLKQGWTPRRMFKEADDFFTSLGLLPVPPEFW
mu-ACE      NMWAQTWSNIYDLVAPFPSAPNIDATEAMIKQGWTPRRIFKEADNFFTSLGLLPVPPEFW
rat-ACE     NMWAQTWSNIYDLVAPFPSAPSIDATEAMIKQGWTPRRIFKEADNFFTSLGLLPVPPEFW
rb-ACE      NMWAQTWSNIYDLVAPFPSASTMDATEAMIKQGWTPRRMFEEADKFFISLGLLPVPPEFW
            :**.: *:*:*.*..** . ..:*.*:***:.*.* .:*:*:***:.** *:**  :.  **

ace-2       ENSMLTDPGNVQKAVCHPTAWDLGKG-DFRILMCTKVTMDDFLTAHHEMGHIQYDMAYAA
hu-ACET     NKSMLEKPTDGREVVCHASAWDFYNGKDFRIKQCTTVNLEDLVVAHHEMGHIQYFMQYKD
mu-ACET     NKSMLEKPTDGREVVCHPSAWDFYNGKDFRIKQCTSVNMEDLVIAHHEMGHIQYFMQYKD
rb-ACET     NKSMLEKPTDGREVVCHASAWDFYNGKDFRIKQCTTVNMEDLVVVHHEMGHIQYFMQYKD
hu-ACE      NKSMLEKPTDGREVVCHASAWDFYNGKDFRIKQCTTVNLEDLVVAHHEMGHIQYFMQYKD
mu-ACE      NKSMLEKPTDGREVVCHPSAWDFYNGKDFRIKQCTSVNMEDLVIAHHEMGHIQYFMQYKD
rat-ACE     NKSMLEKPTDGREVVCHASAWDFYNGKDFRIKQCTSVNMEELVIAHHEMGHIQYFMQYKD
rb-ACE      NKSMLEKPTDGREVVCHASAWDFYNGKDFRIKQCTTVNMEDLVVVHHEMGHIQYFMQYKD
            ::*** .* : ::.***.:***: :* **** **.*.:::::: .********* * *

ace-2       QPFLLRNGANEGFHEAVGEIMSLSAATPKHLKSIGLLSPDFQEDNETEINFLLKQALTIV
hu-ACET     LPVALREGANPGFHEAIGDVLALSVSTPKHLHSLNLLSSEGGSD-EHDINFLMKMALDKI
mu-ACET     LPVTFREGANPGFHEAIGDIMALSVSTPKHLYSLNLLSTEGSGY-EYDINFLMKMALDKI
rb-ACET     LPVALREGANPGFHEAIGDVLALSVSTPKHLHSINLLSSEGGGY-EHDINFLMKMALDKI
hu-ACE      LPVALREGANPGFHEAIGDVLALSVSTPKHLHSLNLLSSEGGSD-EHDINFLMKMALDKI
mu-ACE      LPVTFREGANPGFHEAIGDIMALSVSTPKHLYSLNLLSTEGSGY-EYDINFLMKMALDKI
rat-ACE     LPVTFREGANPGFHEAIGDVLALSVSTPKHLHSLNLLSSEGSGY-EHDINFLMKMALDKI
rb-ACE      LPVALREGANPGFHEAIGDVLALSVSTPKHLHSINLLSSEGGGY-EHDINFLMKMALDKI
             *. :*:*** *****:*::::**.:***** *:.***.:      * :****:* **  :

ace-2       GTLPFTYMLEKWRWMVFKGEIPKDQWMKKWWEMKREIVGVVEPVPHDETYCDPASLFHVS
hu-ACET     AFIPFSYLVDQWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPVPRTQGDFDPGAKFHIP
mu-ACET     AFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPVPRSQGDFDPGSKFHVP
rb-ACET     AFIPFSYLVDEWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPAPRSQGDFDPGAKFHIP
hu-ACE      AFIPFSYLVDQWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPVPRTQGDFDPGAKFHIP
mu-ACE      AFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPVPRSQGDFDPGSKFHVP
rat-ACE     AFIPFSYLIDQWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPVPRSQGDFDPGSKFHVP
rb-ACE      AFIPFSYLVDEWRWRVFDGSITKENYNQEWWSLRLKYQGLCPPAPRSQGDFDPGAKFHIP
            . :**:*::::*** **.*.*.*::: ::**.:: :  *:  *.*: :   **.: **:.

ace-2       NDYSFIRYYTRTLYQFQFQEALCQAAKHEGPLHKCDISNSTEAGQKLFNMLRLGKSEPWT
hu-ACET     SSVPYIRYFVSFIIQFQFHEALCQAAGHTGPLHKCDIYQSKEAGQRLATAMKLGFSRPWP
mu-ACET     ANVPYVRYFVSFIIQFQFHEALCRAAGHTGPLHKCDIYQSKEAGKLLADAMKLGYSKPWP
rb-ACET     SSVPYIRYFVSFIIQFQFHEALCKAAGHTGPLHTCDIYQSKEAGKRLADAMKLGYSKPWP
hu-ACE      SSVPYIRYFVSFIIQFQFHEALCQAAGHTGPLHKCDIYQSKEAGQRLATAMKLGFSRPWP
mu-ACE      ANVPYVRYFVSFIIQFQFHEALCRAAGHTGPLHKCDIYQSKEAGKLLADAMKLGYSKPWP
rat-ACE     ANVPYIRYFISFIIQFQFHEALCRAAGHTGPLYKCDIYQSKEAGKLLADAMKLGYSKQWP
rb-ACE      SSVPYIRYFVSFIIQFQFHEALCKAAGHTGPLHTCDIYQSKEAGKRLADAMKLGYSKPWP
             . .::**:   : ****:****:** * ***:.*** :*.***: *   ::** *: *.

ace-2       LALENVVGAKNMNVRPLLNYFEPLFTWLKDQNKNSFVGWSTDWSPYADQSIKVRISLKSA
hu-ACET     EAMQLITGQPNMSASAMLSYFKPLLDWLRTENEL----------------------HGEK
mu-ACET     EAMKLITGQPNMSASAMMNYFKPLTEWLVTENRR----------------------HGET
rb-ACET     EAMKVITGQPNMSASAMMNYFKPLMDWLLTENGR----------------------HGEK
hu-ACE      EAMQLITGQPNMSASAMLSYFKPLLDWLRTENEL----------------------HGEK
mu-ACE      EAMKLITGQPNMSASAMMNYFKPLTEWLVTENRR----------------------HGET
rat-ACE     EAMKIITGQPNMSASAIMNYFKPLTEWLVTENRR----------------------HGET
rb-ACE      EAMKVITGQPNMSASAMMNYFKPLMDWLLTENGR----------------------HGEK
             *:: :.*  **.. .::.**:**  **  :*                          .
```

Figure 2 (D)

```
ace-2       LGDK[redacted]NEMYLFRSSVAYAMRQYFLKVKNQMILFGEEDVR[redacted]RISENFFVTA
hu-ACET     LGWPQY[redacted]PN----------[redacted]----------
mu-ACET     LGWPEYNWAPN----------
rb-ACET     LGWPQYTWTPN----------
hu-ACE      LGWPQYNWTPN----------
mu-ACE      LGWPEYNWAPN----------
rat-ACE     LGWPEYTWTPN----------
rb-ACE      LGWPQYTWTPN----------
            **   * *  *

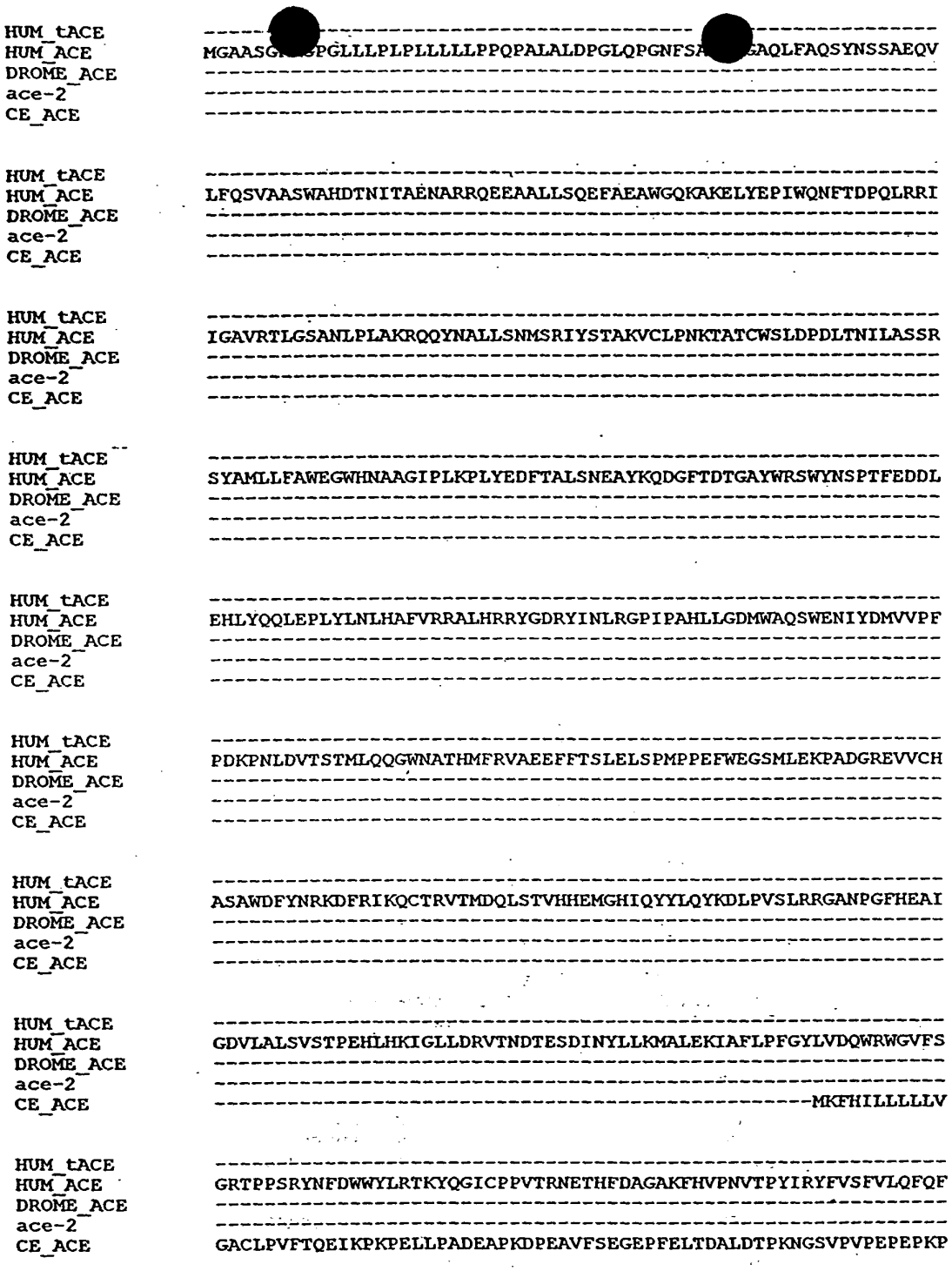
ace-2       PKNVSDIIPRTEVEKAIRMSRSRINDAFRLNDNSLEFLGIQPTLGPPNQPPVSIWLIVFG
hu-ACET     -------SARSE---------GPLPDSGRVS-----FLGLDLD---AQQARVGQWLLLFL
mu-ACET     -------TARAE---------GSTAESNRVN-----FLGLYLE---PQQARVGQWVLLFL
rb-ACET     -------SARSE---------GSLPDSGRVN-----FLGMNLD---AQQARVGQWVLLFL
hu-ACE      -------SARSE---------GPLPDSGRVS-----FLGLDLD---AQQARVGQWLLLFL
mu-ACE      -------TARAE---------GSTAESNRVN-----FLGLYLE---PQQARVGQWVLLFL
rat-ACE     -------TARAE---------GSLPESSRVN-----FLGMYLE---PQQARVGQWVLLFL
rb-ACE      -------SARSE---------GSLPDSGRVN-----FLGMNLD---AQQARVGQWVLLFL
                    .*:*          .   :: *:.     ***:      .:*. *. *:::*

ace-2       VVMGVIVVGIVILIFTGIRDRKKKNKARSGENPYASIDISKGENNPGFQNTDDVQTSFN
hu-ACET     GIALLVATLGLSQRLFSIR-HRSLHRHSHG---------------PQFGSEVELRHS--
mu-ACET     GVALLVATVGLAHRLYNIRNHHSLRRPHRG---------------PQFGSEVELRHS--
rb-ACET     GVALLLASLGLTQRLFSIR-YQSLRQPHHG---------------PQFGSEVELRHS--
hu-ACE      GIALLVATLGLSQRLFSIR-HRSLHRHSHG---------------PQFGSEVELRHS--
mu-ACE      GVALLVATVGLAHRLYNIRNHHSLRRPHRG---------------PQFGSEVELRHS--
rat-ACE     GVALLVATVGLAHRLYNIHNHHSLRRPHRG---------------PQFGSEVELRHS--
rb-ACE      GVALLLASLGLTQRLFSIR-YQSLRQPHHG---------------PQFGSEVELRHS--
             :  ::.   :   : .*:  :. .:   *                * * .  ::: *
```

TMD

09680-0545US

Figure 3 (A)




09535901.080600

Figure 3 (B)

```
HUM_tACE        ------------------------------------MGQGWATAGLPSLLFLLLCYGHPLL
HUM_ACE         HEALCKEAGYEGPLHQCDIYRSTKAGAKLRKVLQAGSSRPWQEVLKDMVGLDALDAQPLL
DROME_ACE       ------------------------------------------------------------
ace-2           ------------------------------------------------------------
CE_ACE          EPEPEPEPKPEPEPSPTPEPEPAIKFDNIESEDYGDVAETAASTQPDELNTEVIEQLVDT

HUM_tACE        VPSQEASQQVTVTHGTSSQATTSSQTTTHQATAHQTSAQSPNLVTDEAEASKFVEEYDRT
HUM_ACE         KYFQPVTQWLQEQNQQNGEVLGWPEYQWHPPLPDNYPEG-IDLVTDEAEASKFVEEYDRT
DROME_ACE       ------------------------MRLFLLALLATLAVTQALVKEEIQAKEYLENLNKE
ace-2           ------------------------MSSSSWLLLSLVAVTAAQSTIEEQAKTFLDKFNHE
CE_ACE          FLNTGSIASNKTNKGPVFANPVAQALVNSSNYWKTDNLQAPGSIKDEEKLRSWLAGYEAE

HUM_tACE        SQVVWNEYAEANWNYNTNITTETSKILLQKNMQIANHTLKYGTQARKFDVNQLQNTTIKR
HUM_ACE         SQVVWNEYAEANWNYNTNITTETSKILLQKNMQIANHTLKYGTQARKFDVNQLQNTTIKR
DROME_ACE       LAKRTNVETEAAWAYGSNITDENEKKKNEISAELAKFMKEVASDTTKFQWRSYQSEDLKR
ace-2           AEDLFYQSSLASWNYNTNITEENVQNMNNAGDKWSAFLKEQSTLAQMYPLQEIQNLTVKL
CE_ACE          AIKVLREVALSGWRYFNDASPSLKLALDEAENVLTMFVRSTSMQAKQFDMASVTDEKVMR

HUM_tACE        IIKKVQDLERAALPAQELEEYNKILLDMETTYSVATVCHPNGS---CLQLEPDLTNVMAT
HUM_ACE         IIKKVQDLERAALPAQELEEYNKILLDMETTYSVATVCHPNGS---CLQLEPDLTNVMAT
DROME_ACE       QFKALTKLGYAALPEDDYAELLDTLSAMESNFAKVKVCDYKDSTKCDLALDPEIEEVISK
ace-2           QLQALQQNGSSVLSEDKSKRLNTILNTMSTIYSTGKVCNPDNPQE-CLLLEPGLNEIMAN
CE_ACE          QLGYVSFEGMSALAPSRFADYSQAQAALNRDSKDSTICDKDVPPP-CALQKIDMDSIFRN

HUM_tACE        SRKYEDLLWAWEGWRDKAGRAILQFYPKYVELINQAARLNGYVDAGDSWRSMYETP----
HUM_ACE         SRKYEDLLWAWEGWRDKAGRAILQFYPKYVELINQAARLNGYVDAGDSWRSMYETP----
DROME_ACE       SRDHEELAYYWREFYDKAGTAVRSQFERYVELNTKAAKLNNFTSGAEAWLDEYEDD----
ace-2           SLDYNERLWAWESWRSEVGKQLRPLYEEYVVLKNEMARANHYEDYGDYWRGDYEVNGVDG
CE_ACE          EKDASRLQHLWVSYVTAIAKSK-PSYNNIITISNEGAKLNGFANGGAMWRSAFDMSS--K

HUM_tACE        ------SLEQDLERLFQELQPLYLNLHAYVRRALHRHYG-AQHINLEGPIPAHLLGNMWA
HUM_ACE         ------SLEQDLERLFQELQPLYLNLHAYVRRALHRHYG-AQHINLEGPIPAHLLGNMWA
DROME_ACE       ------TFEQQLEDIFADIRPLYQQIHGYVRFRLRKHYG-DAVVSETGPIPMHLLGNMWA
ace-2           YDYSRGQLIEDVEHTFEEIKPLYEHLHAYVRAKLMNAY--PSYISPIGCLPAHLLGDMWG
CE_ACE          VHKAEFDLNKQIDKIYSTIQPFYQLLHAYMRRQLAGIYSNPVGLSKDGPIPAHLFGSLDG

HUM_tACE        QTWSNIYDLVVPFPSA--PSMDTTEAMLKQGWTPRRMFKEADDFFTSLGLLPVPPEFWNK
HUM_ACE         QTWSNIYDLVVPFPSA--PSMDTTEAMLKQGWTPRRMFKEADDFFTSLGLLPVPPEFWNK
DROME_ACE       QQWSEIADIVSPFPEK--PLVDVSAEMEKQAYTPLKMFQMGDDFFTSMNLTKLPQDFWDK
ace-2           RFWTNLYSLTVPFGQK--PNIDVTDAMVDQAWDAQRIFKEAEKFFVSVGLPNMTQGFWEN
CE_ACE          GDWSAHYEQTKPFEEESETPEAMLSAFNTQNYTTKKMFVTAYRYFKSAGFPHLPKSYWTS

HUM_tACE        SMLEKPTDGREVVCHAS-AWDFYNGKDFRIKQCTTVNLEDLVVAHHEMGHIQYFMQYKDL
HUM_ACE         SMLEKPTDGREVVCHAS-AWDFYNGKDFRIKQCTTVNLEDLVVAHHEMGHIQYFMQYKDL
DROME_ACE       SIIEKPTDGRDLVCHAS-AWDFYLIDDVRIKQCTRVTQDQLFTVHHELGHIQYFLQYQHQ
ace-2           SMLTDPGNVQKAVCHPT-AWDLGKG-DFRILMCTKVTMDDFLTAHHEMGHIQYDMAYAAQ
CE_ACE          SIFAR-VWSKDMICHPAAALDMRAPNDFRVKACAQLGEPDFEQAHSLLVQTYYQYLYKDQ

HUM_tACE        PVALREGANPGFHEAIGDVLALSVSTPKHLHSLNLLSSEGGSD--EHDINFLMKMALDKI
HUM_ACE         PVALREGANPGFHEAIGDVLALSVSTPKHLHSLNLLSSEGGSD--EHDINFLMKMALDKI
DROME_ACE       PFVYRTGANPGFHEAVGDVLSLSVSTPKHLEKIGLLKDYVRDD--EARINQLFLTALDKI
ace-2           PFLLRNGANEGFHEAVGEIMSLSAATPKHLKSIGLLSPDFQEDN-ETEINFLLKQALTIV
CE_ACE          SLLFREQASPVITDAIANAFAHLSTNPHYLYSQKLVPSEHLDIKDSVIINKLYKESLESF
```

0005005.1005550

Figure 3 (C)

```
HUM_tACE        AFIPE[redacted]QWRWRVFDGSITKENYNQEWWSLRLKYQGL[redacted]RTQGDFDPGAKFHIP
HUM_ACE         AFIPFS[redacted]DQWRWRVFDGSITKENYNQEWWSLRLKYQGLC[redacted]RTQGDFDPGAKFHIP
DROME_ACE       VFLPFAFTMDKYRWSLFRGEVDKANWNCAFWKLRDEYSGIEPPVVRSEKDFDAPAKYHIS
ace-2           GTLPFTYMLEKWRWMVFKGEIPKDQWMKKWWEMKREIVGVVEPVPHDETYCDPASLFHVS
CE_ACE          TKLPFTIAADNWRYELFDGTVPKNKLNDRWWEIRNKYEGVRSPQPYNTSNLDALIHNSVS
                  :**:   :::*: :* * : * :     :*.:: :  *:  *         *.      :.

HUM_tACE        -SSVPYIRYFVSFIIQFQFHEALCQAAGHTG------PLHKCDIYQSKEAGQRLATAMKL
HUM_ACE         -SSVPYIRYFVSFIIQFQFHEALCQAAGHTG------PLHKCDIYQSKEAGQRLATAMKL
DROME_ACE       -ADVEYLRYLVSFIIQFQFYKSACIKAGQYDPDNVELPLDNCDIYGSARAGAAFHNMLSM
ace-2           -NDYSFIRYYTRTLYQFQFQEALCQAAKHEG------PLHKCDISNSTEAGQKLFNMLRL
CE_ACE          QVHSPATRTLISYVLKFQILKALCQRELFWL------SEGCILSEDTT---EKLRETMKL
                        *     : :**: :: *               .        :      :   : :

HUM_tACE        GFSRPWPEAMQLITGQPNMSASAMLSYFKPLLDWLRTEN----------------------
HUM_ACE         GFSRPWPEAMQLITGQPNMSASAMLSYFKPLLDWLRTEN----------------------
DROME_ACE       GASKPWPDALEAFNGERIMSGKAIAEYFEPLRVWLEAEN----------------------
ace-2           GKSEPWTLALENVVGAKNMNVRPLLNYFEPLFTWLKDQNKNSFVGWSTDWSPYADQSIKV
CE_ACE          GSSITWLKALEMISGKGELDAQPLLEYYEPLINWLRNTN----------------------
                * * .*  *:: . *   :.  .: .*::**  **.  *

HUM_tACE        -ELHGEKLGWPQYNWTPNSAR--------------------------------------------
HUM_ACE         -ELHGEKLGWPQYNWTPNSAR--------------------------------------------
DROME_ACE       -IKNNVHIGWTTSNKCVSS----------------------------------------------
ace-2           RISLKSALGDKAYEWNDNEMYLFRSSVAYAMRQYFLKVKNQMILFGEEDVRVANLKPRIS
CE_ACE          -EIDQVVVGWDGEGTPFTVEEIPKTRQPGDGGNGLPSEDRVAFPGGE-------------
                       :*        .

HUM_tACE        ---------------------------SEGPLPDSGRVSFLGLDLDAQQARVG-------Q
HUM_ACE         ---------------------------SEGPLPDSGRVSFLGLDLDAQQARVG-------Q
DROME_ACE       ---------------------------------------------------------------
ace-2           FNFFVTAPKNVSDIIPRTEVEKAIRMSRSRINDAFRLNDNSLEFLGIQPTLGPPNQPPVS
CE_ACE          ------------------CVNGQECLLDSHCNGTICVCNDGLYTLEIGNTFN---CVPGN

HUM_tACE        WLLLFLGIALLVATLGLSQRLFS-IRHR-----------------SLHRHSHGPQFGSEVE
HUM_ACE         WLLLFLGIALLVATLGLSQRLFS-IRHR-----------------SLHRHSHGPQFGSEVE
DROME_ACE       ---------------------------------------------------------------
ace-2           IWLIVFGVVMGVIVVGIVILIFTGIRDRKKKNKARSGENPYASIDISKGENNPGFQNTDD
CE_ACE          PADSGFGDGKGGLVIGLFNNEVTTPEPSAEPEP--TAKTTTKMPPRVRAATSPFSLYLTV

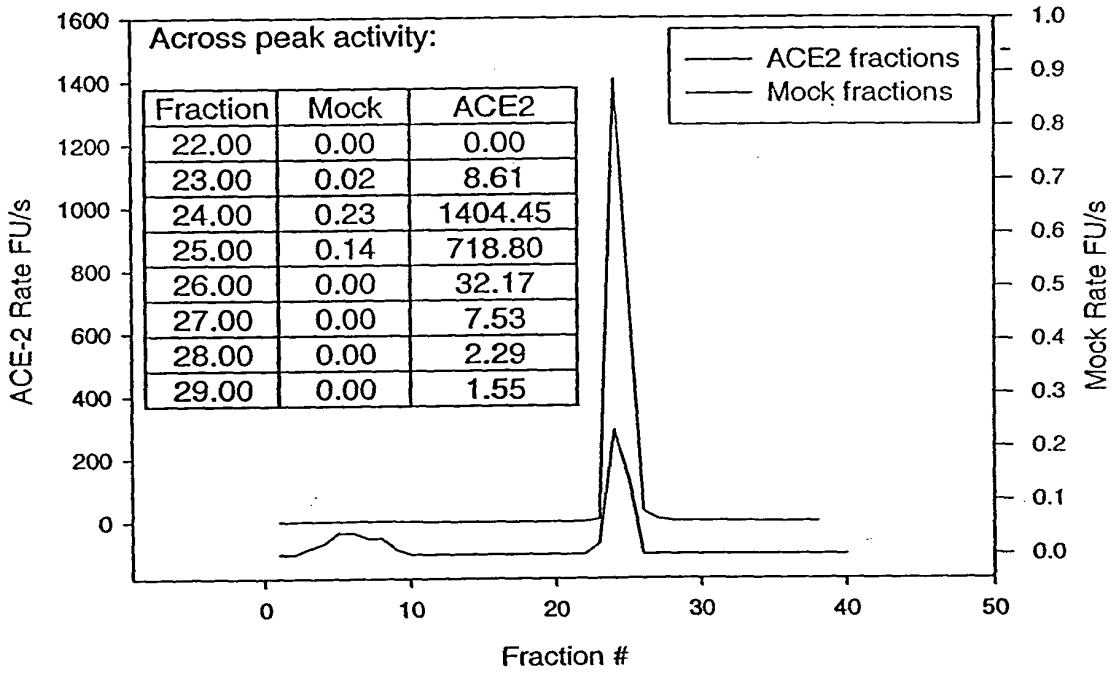
HUM_tACE        LRHS----
HUM_ACE         LRHS----
DROME_ACE       --------
ace-2           VQTSFN--
CE_ACE          LLIIYFAL
```

TMD

09535004.060900

Figure 4

ACE-2 Fractions: Real vs Mocks




| Fraction | Mock | ACE2 |
|---|---|---|
| 22.00 | 0.00 | 0.00 |
| 23.00 | 0.02 | 8.61 |
| 24.00 | 0.23 | 1404.45 |
| 25.00 | 0.14 | 718.80 |
| 26.00 | 0.00 | 32.17 |
| 27.00 | 0.00 | 7.53 |
| 28.00 | 0.00 | 2.29 |
| 29.00 | 0.00 | 1.55 |

0050801-T05546

Figure 5



FIGURE 5A

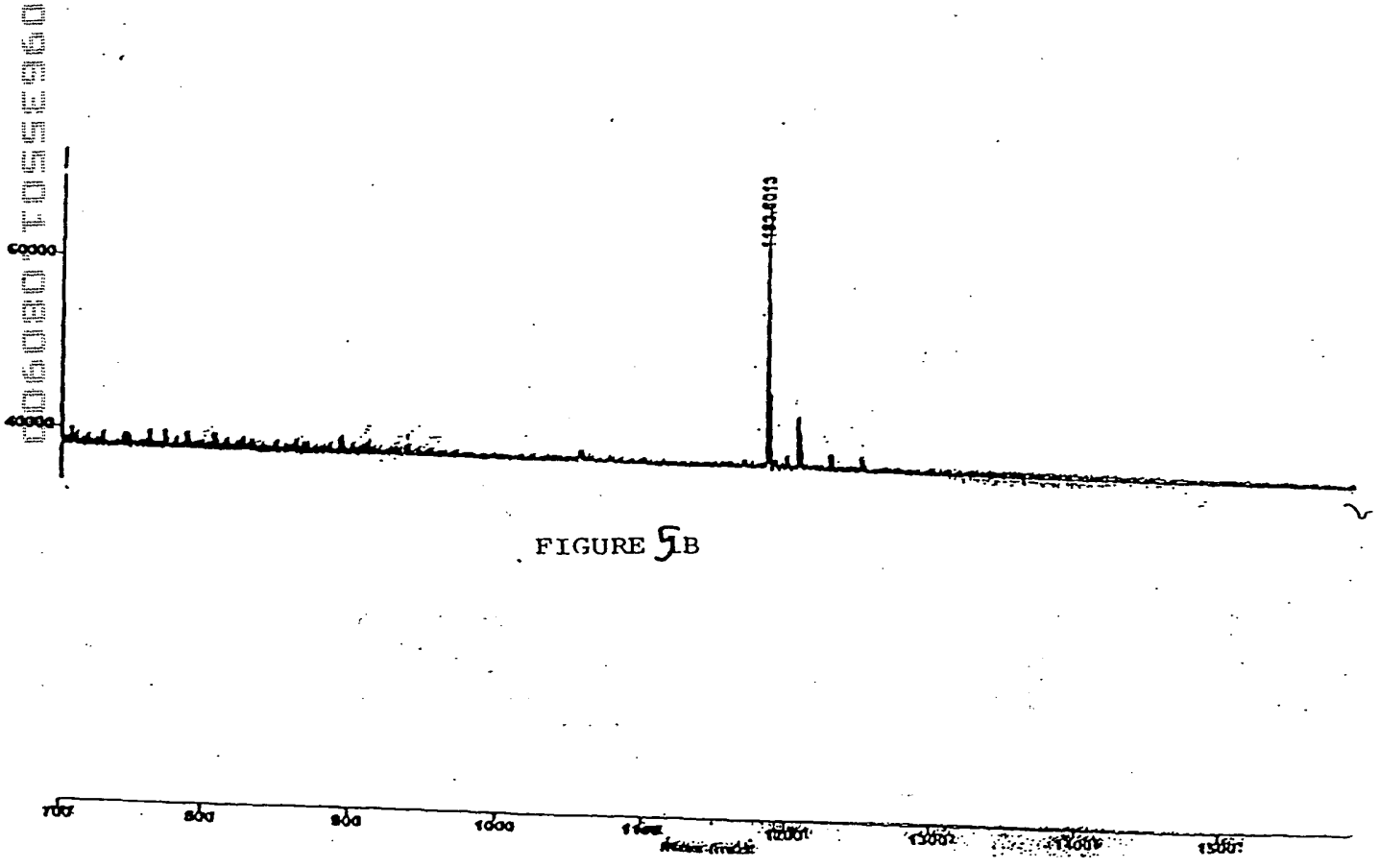


FIGURE 5B

Figure 6

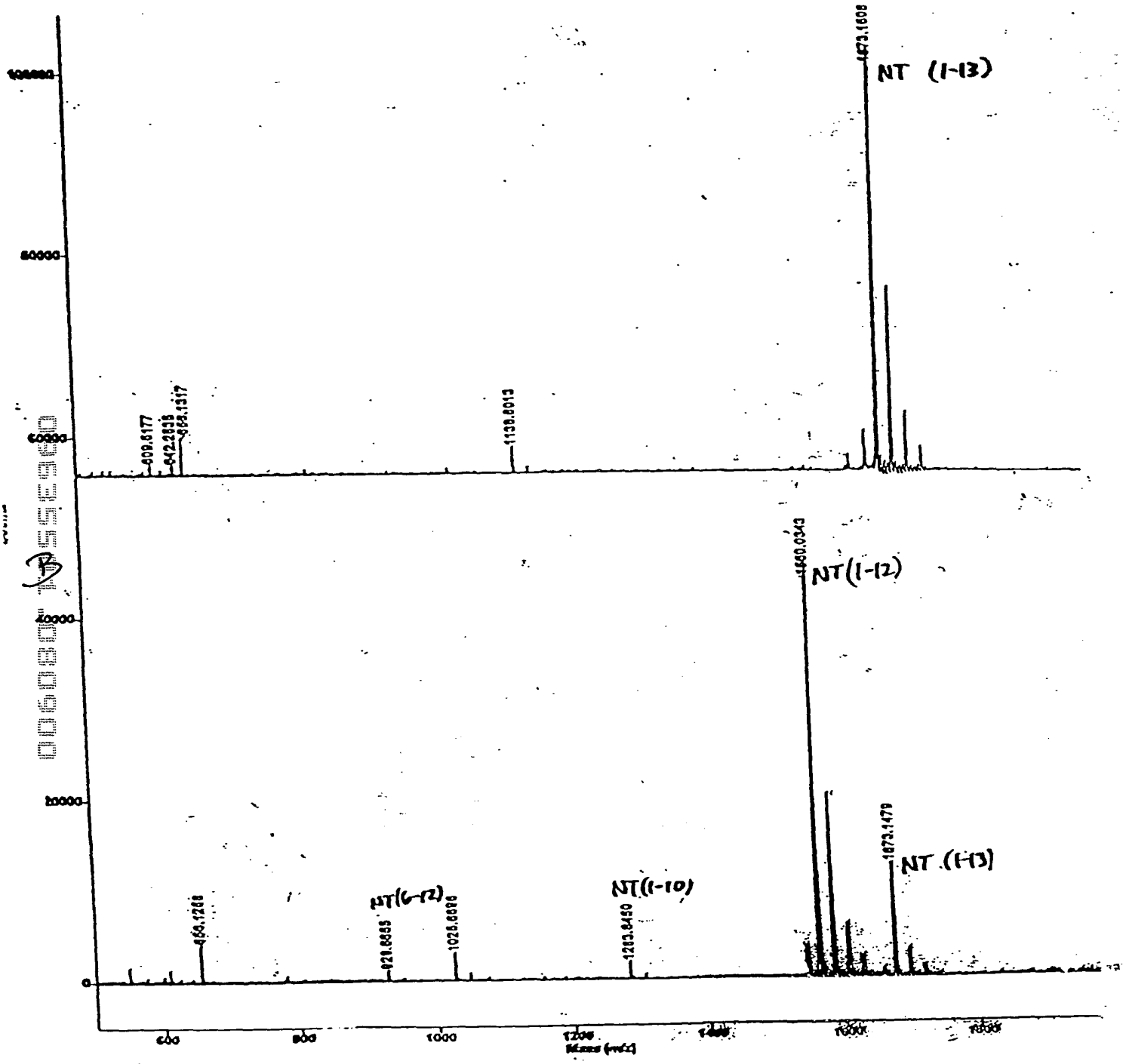



FIGURE 6

Figure 7.

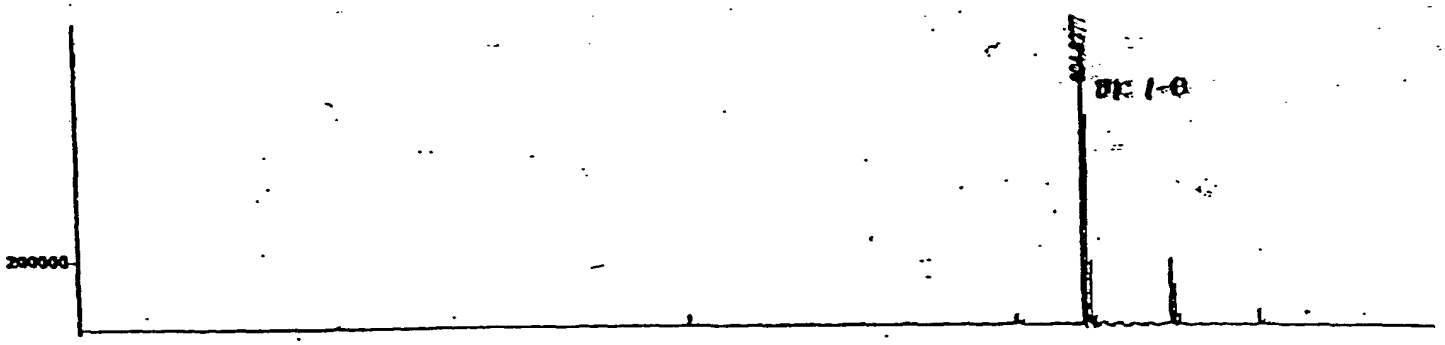



FIGURE 7A

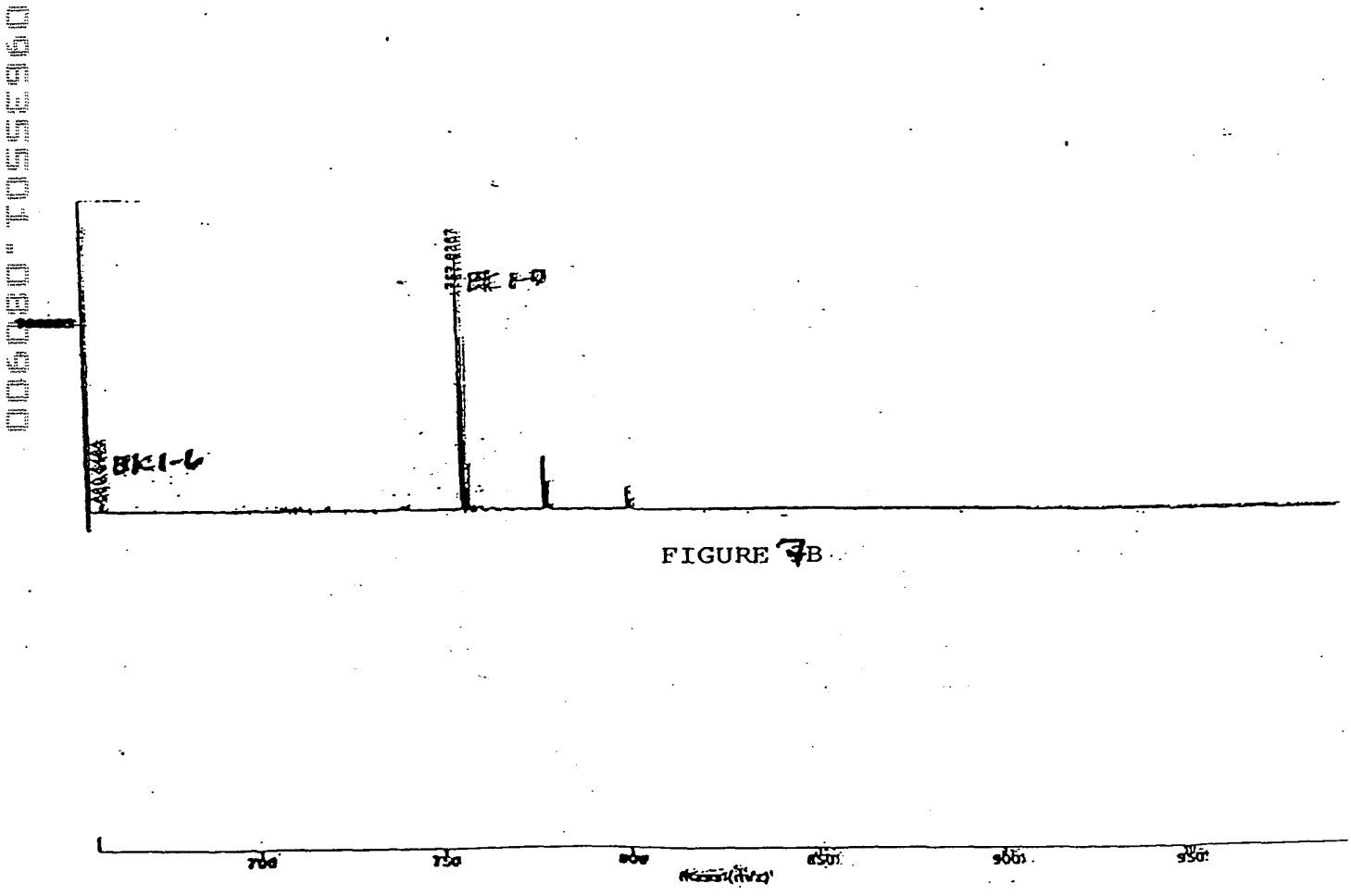



FIGURE 7B

006080" T05SE960

# Angiotensin I conversion to products

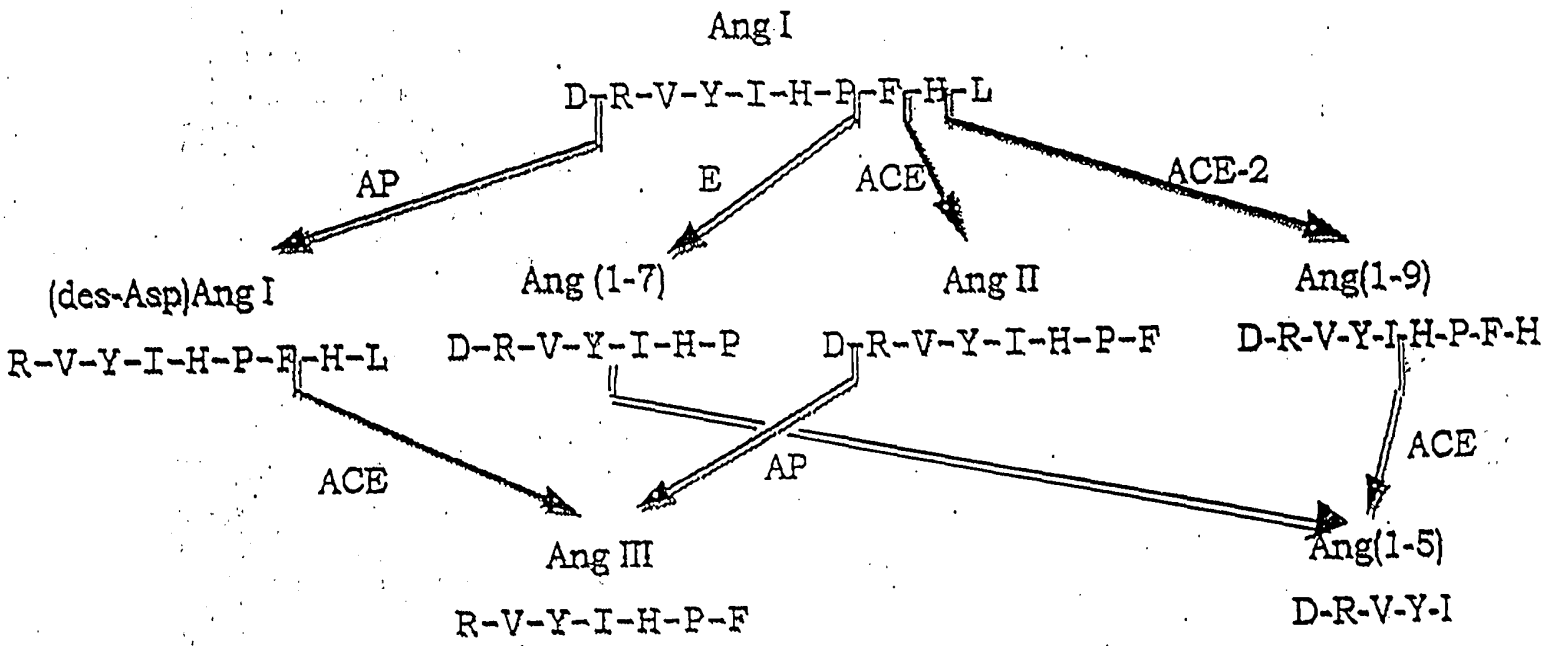
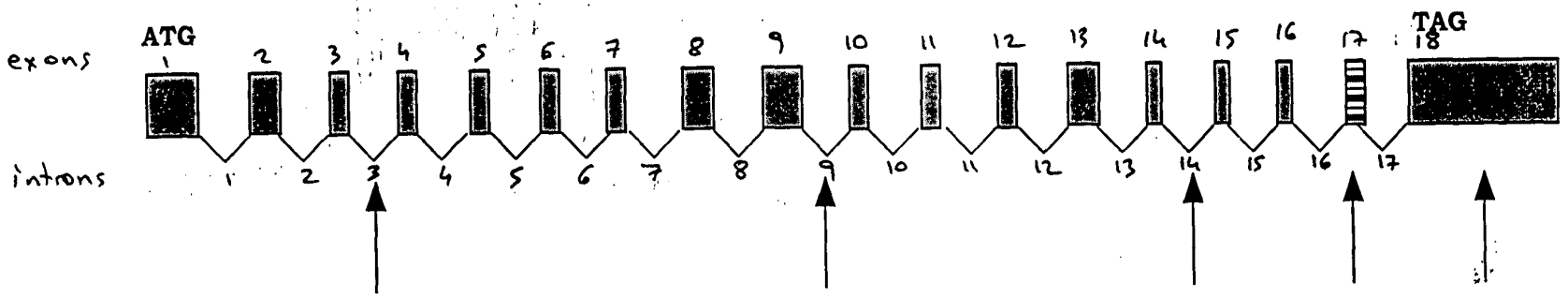



Figure 8

006080" T055E960

# ACE Homologue VARIANTS




ASN → ASP

| G → A | 5 bp insertion (CTTAT) | T → G | 0.016 | G → T |
|---|---|---|---|---|
| 0.250 | 0.396 | 0.010 | | 0.005 |

Figure 9A

# ACE Homologue Variants SEQ ID

GAATTCGGCTTCCATCCTAATACGACTCACTATAGGGCTCGAGCGGCCGCCCGGGGCAGGTATCTTGGCTCACAGGGGACGATGTCAAG
CTCTTCCTGGCTCCTTCTCAGCCTTGTTGCTGTAACTGCTGCTCAGTCCACCATTGAGGAACAGGCCAAGACATTTTTGGACAAGTTTAAC
CACGAAGCCGAAGACCTGTTCTATCAAAGTTCACTTGCTTCTTGGAATTATAACACCAATATTACTGAAGAGAATGTCCAAAACAT /
GAATAATGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAACAGTCCACACTTGCC
CAAATGTATCCACTACAAGAAATTCAGAATCTCACAGTCAAGCTTCAGCTGCAGGCTCTTCAGCAAAATGGGTCTTCAGTGCTCTCAGAA
GACAAGAGCAAACGG / TTGAACACAATTCTAAAT

ACAATGAGCACCATCTACAGTACTGGAAAAGTTTGTAACCCAGATAATCCACAAGAATGCTTATTACTTGAACCAGG /
TTTGAATGAAATAATGGCAAACAGTTTAGACTACAATGAGAGGCTCTGGGC
TTGGGAAAGCTGGAGATCTGAGGTCGGCAAGCAGCTGAGGCCATTATATGAAGAGTATGTGGTCTTGAAAAATGAGATGGCAAGAGCAA
ATC / ATTATGAGGACTATGGGGATTATTGGAGAGGAG
ACTATGAAGTAAATGGGGTAGATGGCTATGACTACAGCCGCGGCCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAG /
ATTAAACCATTATATGAACATCTTCATGCCTATGTGAGGGC
AAAGTTGATGAATGCCTATCCTTCCTATATCAGTCCAATTGGATGCCTCCCTGCTCATTTGCTTGG /
TGATATGTGGGGTAGATTTTGGACAAATCTGTACTCTTTGACAGTTCCCTTTGGACAGAAA
CCAAACATAGATGTTACTGATGCAATGGTGGACCAG / GCCTGGGATGCACAGAGAATATT
CAAGGAGGCCGAGAAGTTCTTTGTATCTGTTGGTCTTCCTAATATGACTCAAGGATTCTGGGAAAATTCCATGCTAACGGACCCAGGAAA
TGTTCAGAAAGCAGTCTGCCATCCCACAGCTTGGGACCTGGG /
GAAGGGCGACTTCAGGATCCTTATGTGCACAAAGGTGACAATGGACGACTTCCTG
ACAGCTCATCATGAGATGGGGCATATCCAGTATGATATGGCATATGCTGCACAACCTTTTCTGCTAAGAAATGGAGCTAATGAAGGATTC
CATGAAGCTGTTGGGGAAATCATGTCACTTTCTGCAGCCACACCTAAGCATTTAAAATCCATTGGTCTTCTGTCACCCGATTTTCAAGAAG
ACAATG / AAACAGAAATAAACTTCCTGCTCAAACAAGCACTCACGATTGTTGGGACTCTGCCATTTACTTA
CATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGGAAATTCCCAAAGACCAGTGGATGAAAAAGTGGTGGGAGATGAAG /
CGAGAGATAGTTGGGGTGGTGGAACCTGTGCCCCATGATGAAA
CATACTGTGACCCCGCATCTCTGTTCCATGTTTCTAATGATTACTCATTCATTCG / ATATTACA
CAAGGACCCTTTACCAATTCCAGTTTCAAGAAGCACTTTGTCAAGCAGCTAAACATGAAGGCCCT
CTGCACAAATGTGACATCTCAAACTCTACAGAAGCTGGACAGAAACTG /
TTCAATATGCTGAGGCTTGGAAAATCAGAACCCTGGACCCTAGCATTGGAAAATGTTGTAGGAGCAAAGAACATGAATGTAAGGCCACT
GCTCAACTACTTTGAGCCCTTATTTACCTGGCTGAAAGACCAGAACAAGAATTCTTTTGTGGGATGGAGTACCGACTGGAGTCC /
ATATGCAGACCAAAGCATCAAAGTGAGGATAAG

CCTAAAATCAGCTCTTGGAGATAAAGC / ATATGAATGGAACGACAATGAAATGTACC
TGTTCCGATCATCTGTTGCATATGCTATGAGGCAGTACTTTTTAAAAGTAAAAAATCAGATGATTCTTTTTGGG /
GAGGAGGATGTGCGAGTGGCTAATTTGAAACCAAGAATCTCCTTTAATTTCTTT
GTCACTGCACCTAAAAATGTGTCTGATATCATTCCTAGAACTGAAGTTGAAAAGGCCATCAGG /
ATGTCCCGGAGCCGTATCAATGATGCTTTCCGTCTGAATGACACAGCCTAGAGTTTCTGGG
GATACAGCCAACACTTGGACCTCCTAACCAGCCCCCTGTTTCCATATGGCTGATTGTTTTTGGAGTTGTGATGGGAGTGATAGTGGTTGG
CATTGTCATCCTGATCTTCACTGGGATCAGAGATCGGAAGAAG /
AAAAATAAAGCAAGAAGTGGAGAAAATCCTTATGCCTCCATCGATATTAGCAAAGGA
GAAAATAATCCAGGATTCCAAAACACTGATGATGTTCAGACCTCCTTTTAGAAAAATCTATGTTTTTCCTCTTGAGGTGATTTTGTTGTATG
TAAATGTTAATTTCATGGTATAGAAAATATAAGATGATAAAGATATCATTAAATGTCAAAACTATGACTCTGTTCAGAAAAAAAATTGTCCA
AAGACAACATGGCCAAGGAGAGAAGCATCTTCATTGACATTGCTTTCAGTATTTATTTCTGTCTCTGGATTTGACTTCTGTTCTGTTTCTTAA
TAAGGATTTTGTATTAGAGTATATTAGGGAAAGTGTGTATTTGGTCTCACAGGCTGTTCAGGGATAATCTAAATGTAAATGTCTGTTGAATT
TCTGAAGTTGAAAACAAGGATATATCATTGGAGCAAGTGTTGGATCTTGTATGGAATATGGATGGATCACTTGTAAGGACAGTGCCTGG
GAACTGGTGTAGCTGCAAGGATTGAGAATGGCATGCATTAGCTCACTTTCATTTAATCCATTGTCAAGGATGACATGCTTTCTTCACAGTA
ACTCAGTTCAAGTACTATGGTGATTTGCCTACAGTGATGTTTGGAATCGATCATGCTTTCTTCAAGGTGACAGGTCTAAAGAGAGAAGAAT
CCAGGGAACAGGTAGAGGACATTGCTTTTTCACTTCCAAGGTGCTTGATCAACATCTCCCTGACAACACAAAACTAGAGCCAGGGGCCT
CCGTGAACTCCCAGAGCATGCCTGATAGAAACTCATTTCTACTGTTCTCTAACTGTGGAGTGAATGGAAATTCCAACTGTATGTTCACCCT
CTGAAGTGGGTACCCAGTCTCTTAAATCTTTTGTATTTGCTCACAGTGTTTGAGCAGTGCTGAGCACAAAGCAGACACTCAATAAATGCTA
GATTTACACACTC / AAAAAAAAAAAAAAAGGGCGGCCGC

**G - A** Intronic
3a/3b

**5 bp insertion** (CTTAT)
Intronic
9a/9b

**T - G** Intronic
14a/14b

**A - G** ASN - ASP
17c/17d

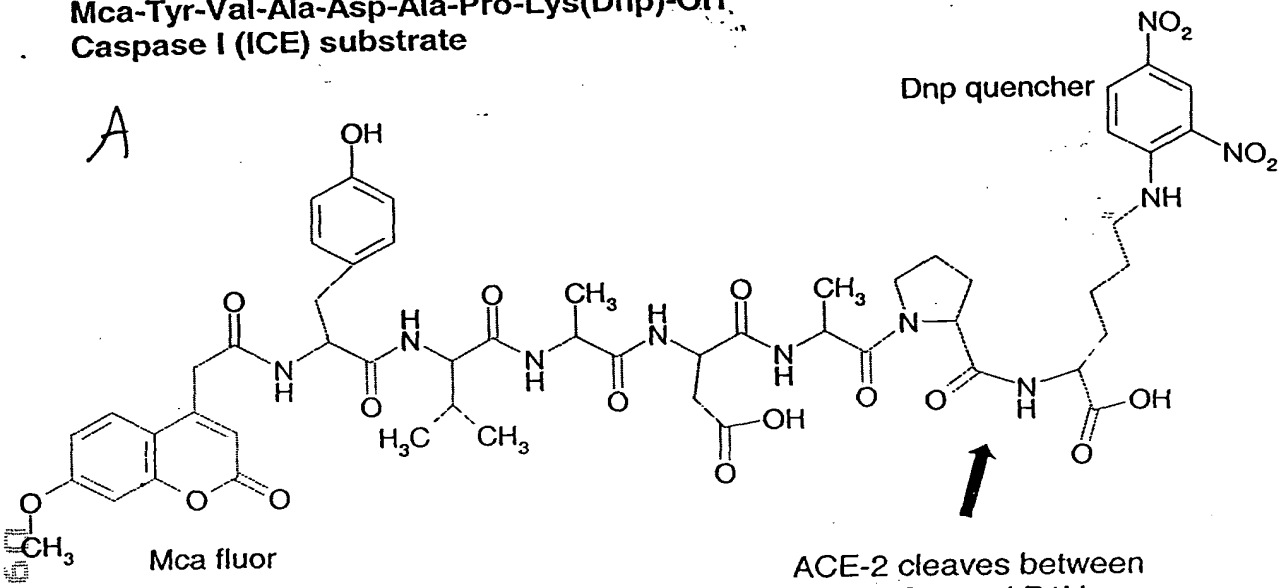
**G - T** 3'UTR
18e/18f

Figure 9B

Figure 10

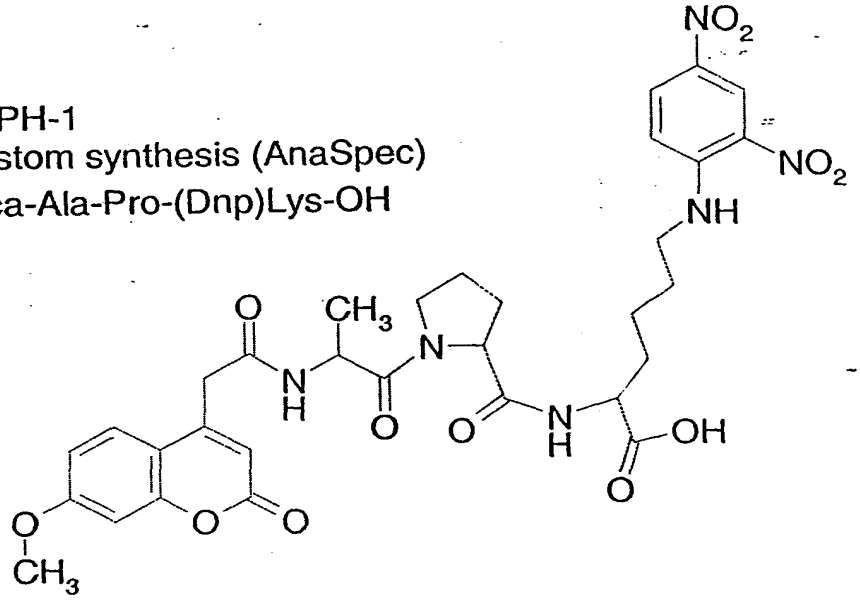
**Bachem M-2195**
**Mca-Tyr-Val-Ala-Asp-Ala-Pro-Lys(Dnp)-OH**
**Caspase I (ICE) substrate**

A



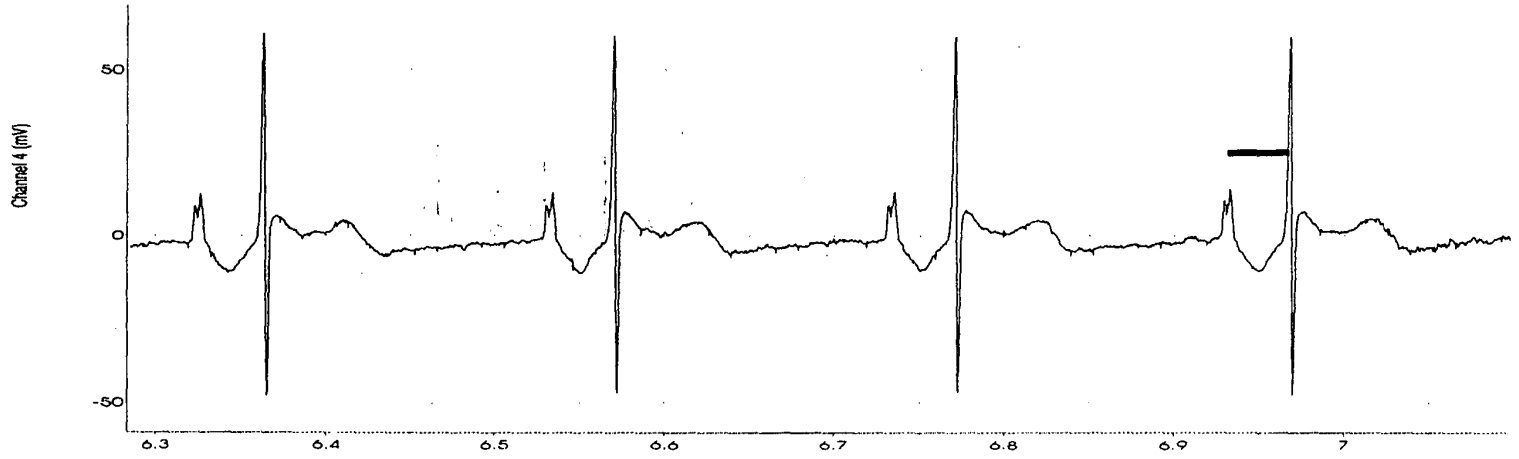

B

MIPH-1
custom synthesis (AnaSpec)
Mca-Ala-Pro-(Dnp)Lys-OH

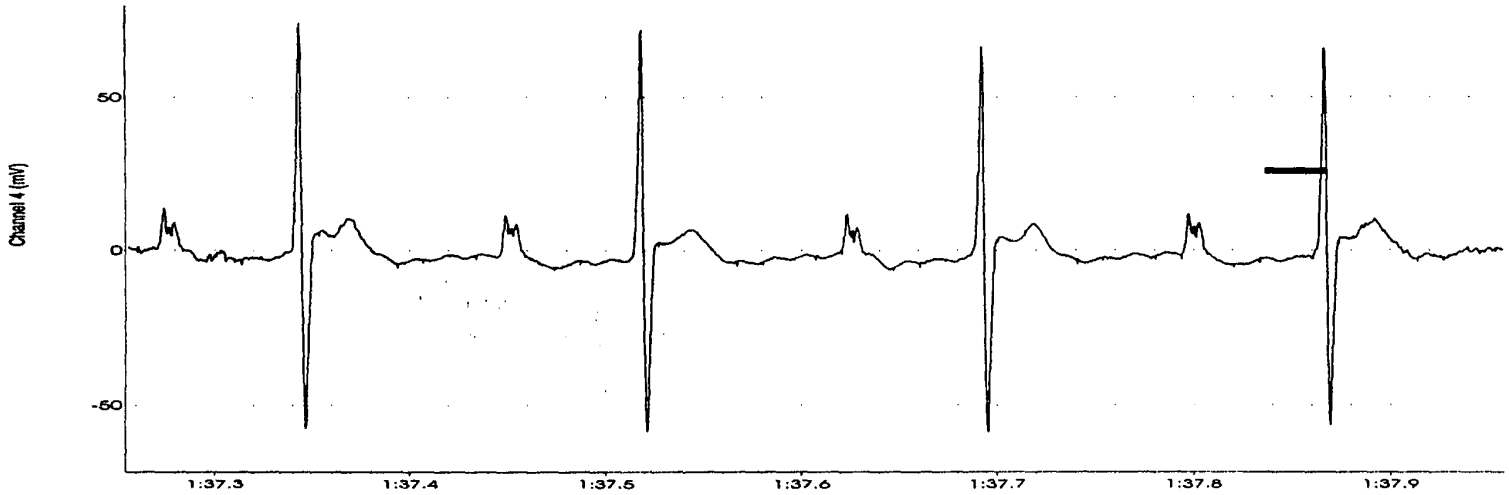


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# Mouse Surface EKG in WT and ACE2 TG Mice




WT (3 day)



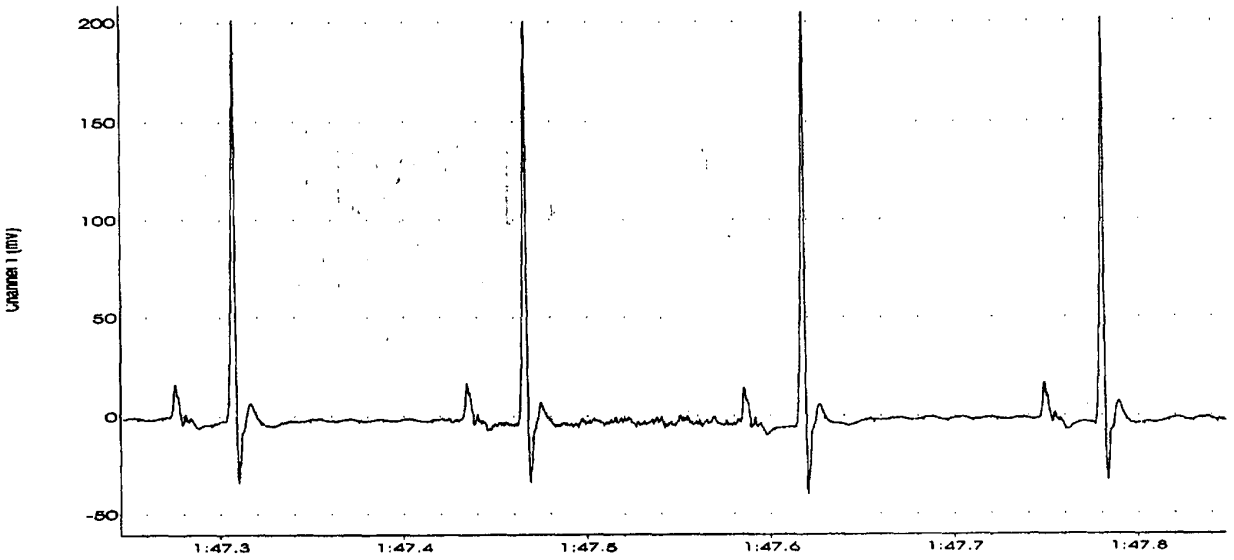

TG (3 day)

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09635501 050900

FIGURE 11A

# Mouse Surface EKG in WT and ACE2 TG Mice




**WT (14 day)**

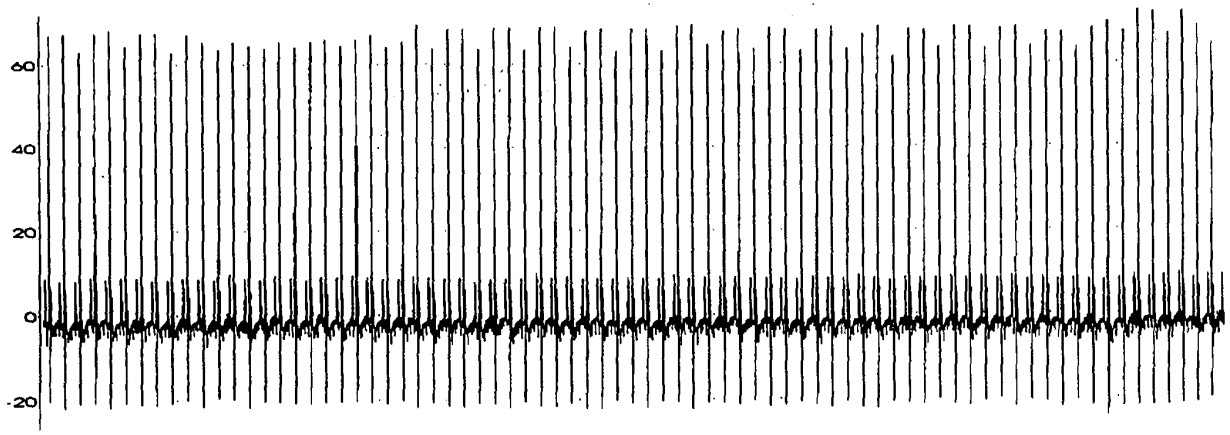


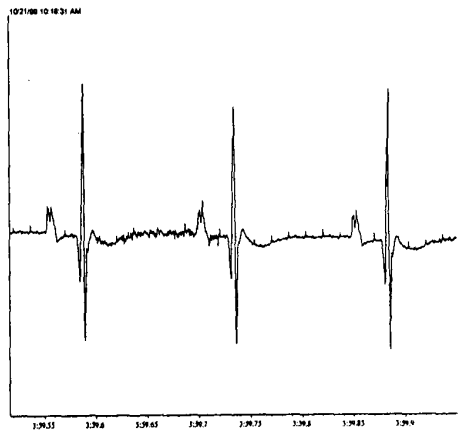

**TG (14 day)**

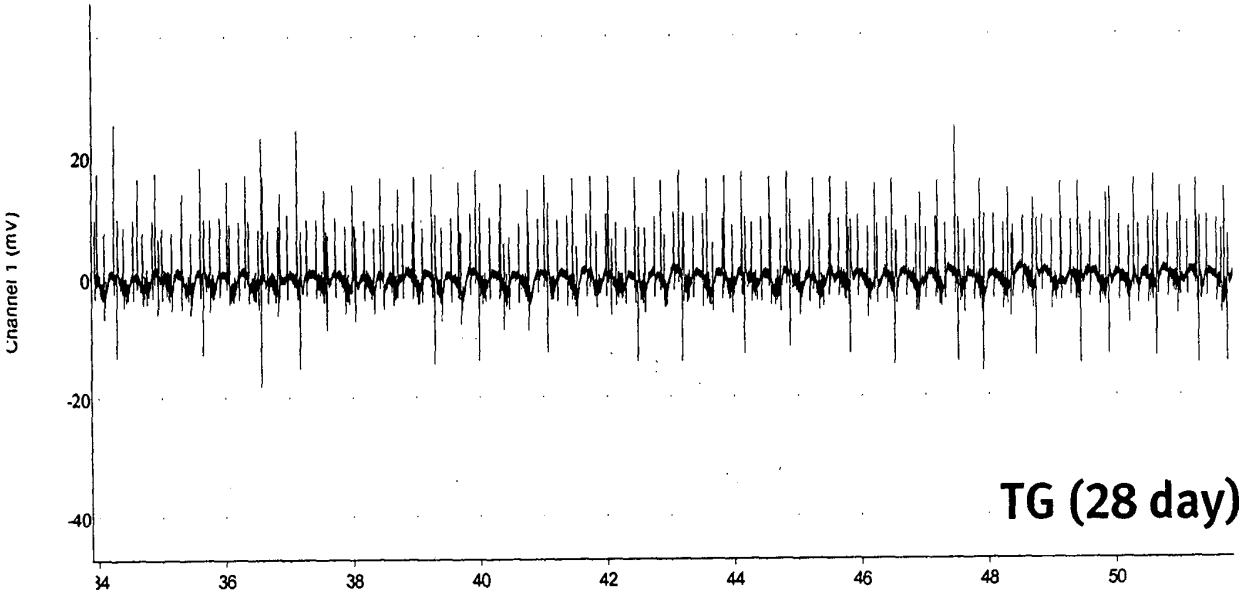
1999 Millennium Pharmaceuticals, Inc.

09635 FIGURE 8B00

# Mouse Surface EKG in WT and ACE2 TG Mice





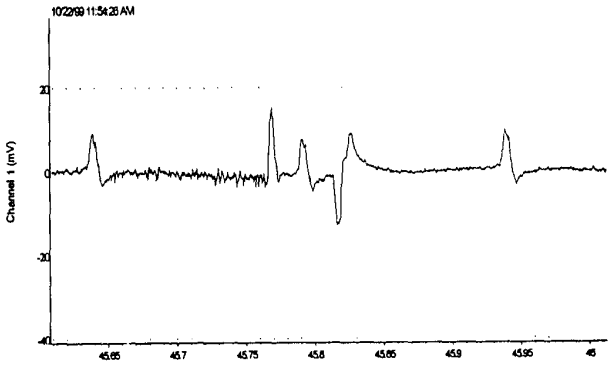
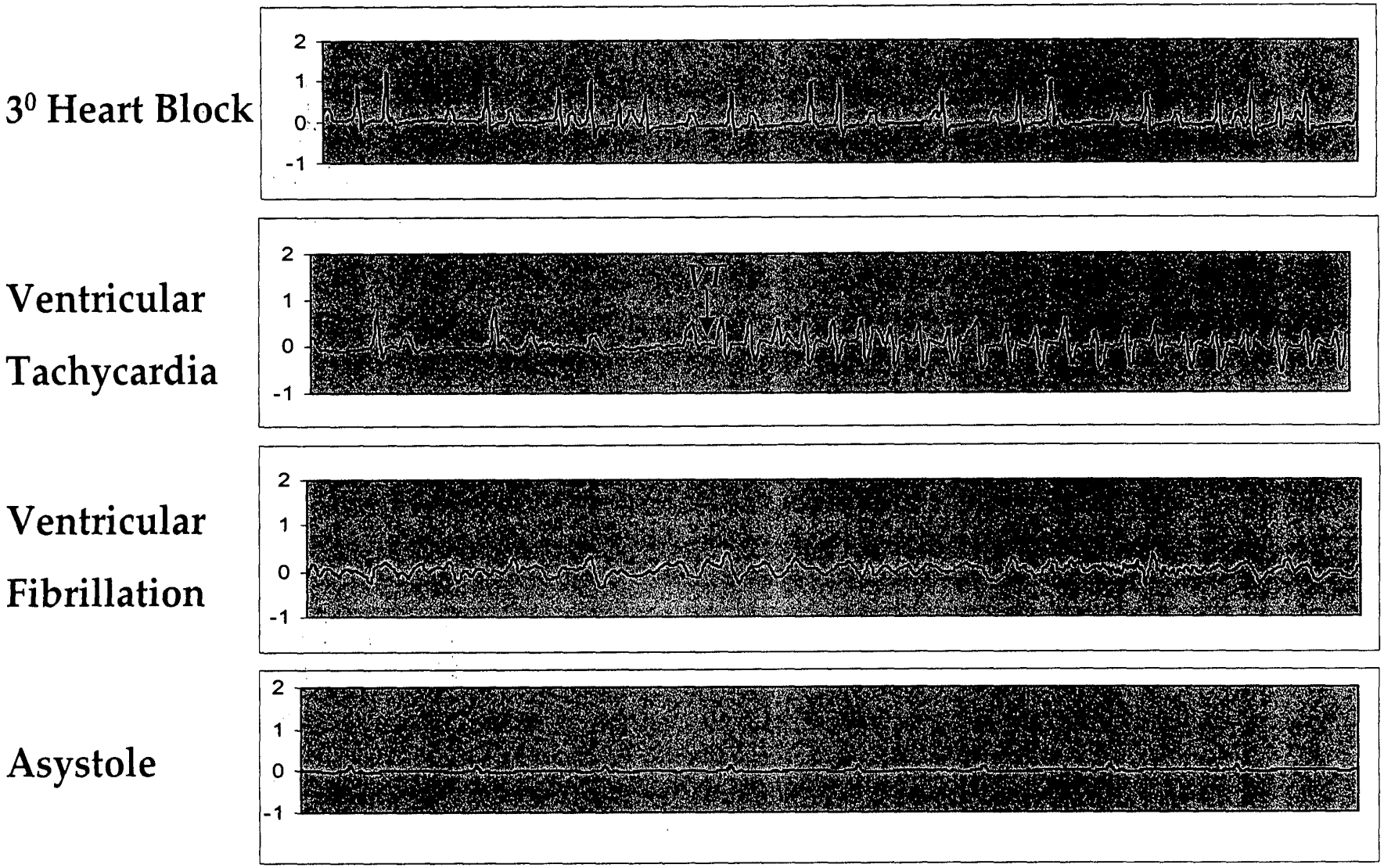




FIGURE 11C

# Sudden Cardiac Death in ACE-2 TG Mice




1999 Miller

09631501.080900

FIGURE 12

# ACE HOMOLOGUE VARIANTS

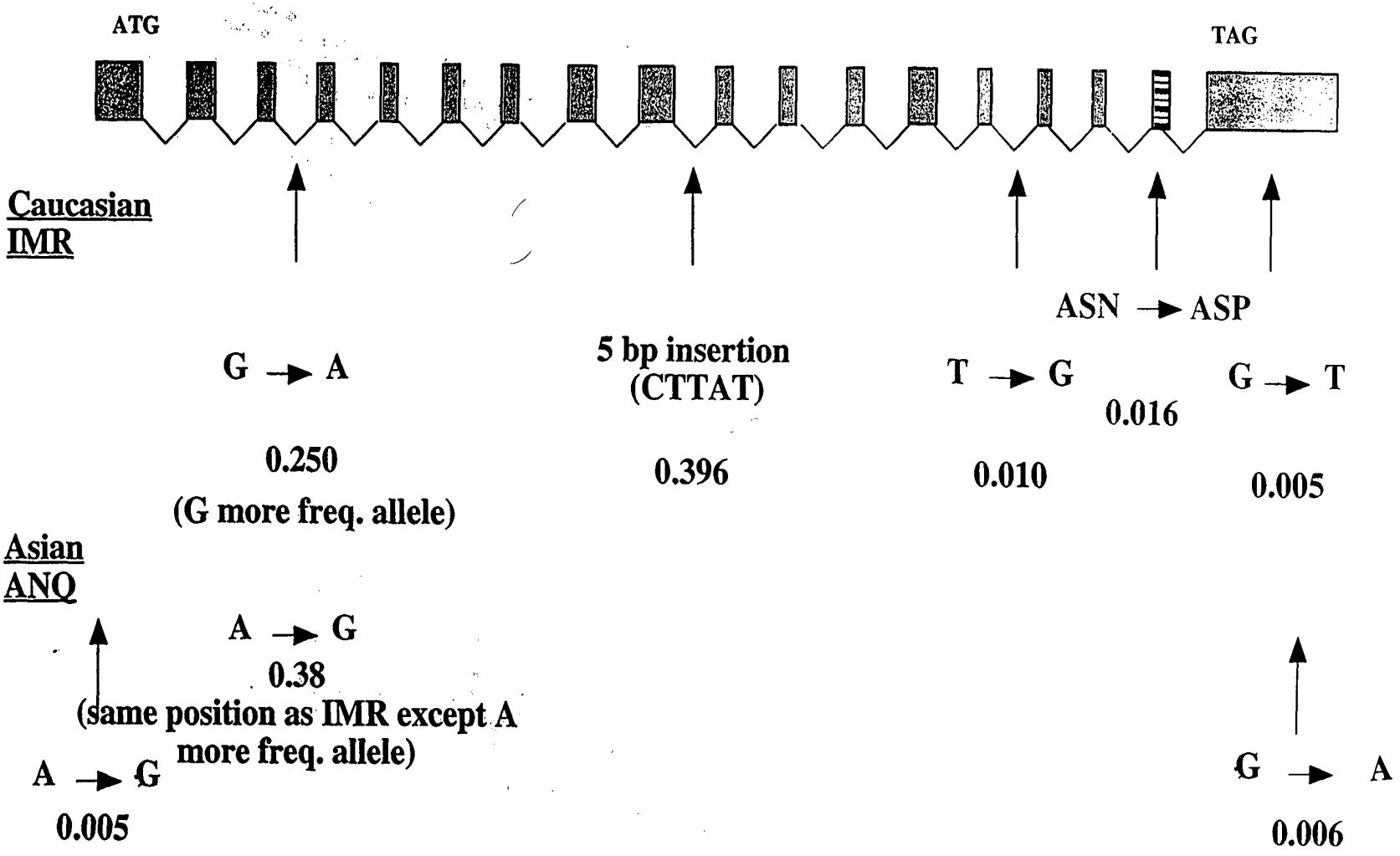



FIGURE 13A

09635501.080900

# ACE Homologue Variants IMR and *ANQ*

GAATTCGGCTTCCATCCTAATACGACTCACTATAGGGCTCGAGCGGCCGCCCGGGGCAGGTATCTTGGCTCACAGGGGACGATGTCAAG
CTCTTCCTGGCTCCTTCTCAGCCTTGTTGCTGTAACTGCTGCTCAGTCCACCATTGAGGAACAGGCCAAGACATTTTTGGACAAGTTTAAC
CACGAAGCCGAAGACCTGTTCTATCAAAGTTCACTTGCTTCTTGGAATTATAACACCAATATTACTGAAGAGAATGTCCAAAACAT /
GAATAATGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAACAGTCCACACTTGCC
CAAATGTATCCACTACAAGAAATTCAGAATCTCACAGTCAAGCTTCAGCTGCAGGCTCTTCAGCAAAATGGGTCTTCAGTGCTCTCAGAA
GACAAGAGCAAACGG / TTGAACACAATTCTAAAT
ACAATGAGCACCATCTACAGTACTGGAAAAGTTTGTAACCCAGATAATCCACAAGAATGCTTATTACTTGAACCAGG /
TTTGAATGAAATAATGGCAAACAGTTTAGACTACAATGAGAGGCTCTGGGC
TTGGGAAAGCTGGAGATCTGAGGTCGGCAAGCAGCTGAGGCCATTATATGAAGAGTATGTGGTCTTGAAAAATGAGATGGCAAGAGCAA
ATC / ATTATGAGGACTATGGGGATTATTGGAGAGGAG
ACTATGAAGTAAATGGGGTAGATGGCTATGACTACAGCCGCGGCCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAG /
ATTAAACCATTATATGAACATCTTCATGCCTATGTGAGGGC
AAAGTTGATGAATGCCTATCCTTCCTATATCAGTCCAATTGGATGCCTCCCTGCTCATTTGCTTGG /
TGATATGTGGGGTAGATTTTGGACAAATCTGTACTCTTTGACAGTTCCCTTTGGACAGAAA
CCAAACATAGATGTTACTGATGCAATGGTGGACCAG / GCCTGGGATGCACAGAGAATATT
CAAGGAGGCCGAGAAGTTCTTTGTATCTGTTGGTCTTCCTAATATGACTCAAGGATTCTGGGAAAATTCCATGCTAACGGACCCAGGAAA
TGTTCAGAAAGCAGTCTGCCATCCCACAGCTTGGGACCTGGG /
GAAGGGCGACTTCAGGATCCTTATGTGCACAAAGGTGACAATGGACGACTTCCTG
ACAGCTCATCATGAGATGGGGCATATCCAGTATGATATGGCATATGCTGCACAACCTTTTCTGCTAAGAAATGGAGCTAATGAAGGATTC
CATGAAGCTGTTGGGGAAATCATGTCACTTTCTGCAGCCACACCTAAGCATTTAAAATCCATTGGTCTTCTGTCACCCGATTTTCAAGAAG
ACAATG / AAACAGAAATAAACTTCCTGCTCAAACAAGCACTCACGATTGTTGGGACTCTGCCATTTACTTA
CATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGGAAATTCCCAAAGACCAGTGGATGAAAAAGTGGTGGGAGATGAAG /
CGAGAGATAGTTGGGGTGGTGGAACCTGTGCCCCATGATGAAA
CATACTGTGACCCCGCATCTCTGTTCCATGTTTCTAATGATTACTCATTCATTCG / ATATTACA
CAAGGACCCTTTACCAATTCCAGTTTCAAGAAGCACTTTGTCAAGCAGCTAAACATGAAGGCCCT
CTGCACAAATGTGACATCTCAAACTCTACAGAAGCTGGACAGAAACTG /
TTCAATATGCTGAGGCTTGGAAAATCAGAACCCTGGACCCTAGCATTGGAAAATGTTGTAGGAGCAAAGAACATGAATGTAAGGCCACT
GCTCAACTACTTTGAGCCCTTATTTACCTGGCTGAAAGACCAGAACAAGAATTCTTTTGTGGGATGGAGTACCGACTGGAGTCC /
ATATGCAGACCAAAGCATCAAAGTGAGGATAAG
CCTAAAATCAGCTCTTGGAGATAAAGC / ATATGAATGGAACGACAATGAAATGTACC
TGTTCCGATCATCTGTTGCATATGCTATGAGGCAGTACTTTTTAAAAGTAAAAAATCAGATGATTCTTTTTGGG /
GAGGAGGATGTGCGAGTGGCTAATTTGAAACCAAGAATCTCCTTTAATTTCTTT
GTCACTGCACCTAAAAATGTGTCTGATATCATTCCTAGAACTGAAGTTGAAAAGGCCATCAGG /
ATGTCCCGGAGCCGTATCAATGATGCTTTCCGTCTGAATGACACAGCCTAGAGTTTCTGGG
GATACAGCCAACACTTGGACCTCCTAACCAGCCCCCTGTTTCCATATGGCTGATTGTTTTTGGAGTTGTGATGGGAGTGATAGTGGTTGG
CATTGTCATCCTGATCTTCACTGGGATCAGAGATCGGAAGAAG /
AAAAATAAAGCAAGAAGTGGAGAAAATCCTTATGCCTCCATCGATATTAGCAAAGGA
GAAAATAATCCAGGATTCCAAAACACTGATGATGTTCAGACCTCCTTTTAGAAAAATCTATGTTTTTCCTCTTGAGGTGATTTTGTTGTATG
TAAATGTTAATTTCATGGTATAGAAAATATAAGATGATAAAGATATCATTAAATGTCAAAACTATGACTCTGTTCAGAAAAAAAATTGTCCA
AAGACAACATGGCCAAGGAGAGAGCATCTTCATTGACATTGCTTTCAGTATTTATTTCTGTCTCTGGATTTGACTTCTGTTCTGTTTCTTAA
TAAGGATTTTGTATTAGAGTATATTAGGGAAAGTGTGTATTTGGTCTCACAGGCTGTTCAGGGATAATCTAAATGTAAATGTCTGTTGAATT
TCTGAAGTTGAAAACAAGGATATATCATTGGAGCAAGTGTTGGATCTTGTATGGAATATGGATGGATCACTTGTAAGGACAGTGCCTGG
GAACTGGTGTAGCTGCAAGGATTGAGAATGGCATGCATTAGCTCACTTTCATTTAATCCATTGTCAAGGATGACATGCTTTCTTCACAGTA
ACTCAGTTCAAGTACTATGGTGATTTGCCTACAGTGATGTTTGGAATCGATCATGCTTTCTTCAAGGTGACAGGTCTAAAGAGAGAAGAAT
CCAGGGAACAGGTAGAGGACATTGCTTTTTCACTTCCAAGGTGCTTGATCAACATCTCCCTGACAACACAAAACTAGAGCCAGGGGCCT
CCGTGAACTCCCAGAGCATGCCTGATAGAAACTCATTTCTACTGTTCTCTAACTGTGGAGTGAATGGAAATTCCAACTGTATGTTCACCCT
CTGAAGTGGGTACCCAGTCTCTTAAATCTTTTGTATTTGCTCACAGTGTTTGAGCAGTGCTGAGCACAAAGCAGACACTCAATAAATGCTA
GATTTACACACTC / AAAAAAAAAAAAAAAGGGCGGCCGC

**A - G** *Intronic*
1c/1d

**G - A** Intronic
**A - G** *Intronic*
3a/3b

**5 bp insertion** (CTTAT)
Intronic
9a/9b

**T - G** Intronic
14a/14b

A - G ASN - ASP
17c/17d

**A - G** *3'UTR*
18c/18d

**G - T** 3'UTR
18e/18f

FIGURE 13B